PUBLICATIONS
FROM THE
ROBERT DAWSON EVANS MEMORIAL
FOR
CLINICAL RESEARCH AND PREVENTATIVE MEDICINE

ENDOCRINE STUDIES

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COLLECTED PUBLICATIONS

from the

ROBERT DAWSON EVANS MEMORIAL

for

CLINICAL RESEARCH AND PREVENTATIVE MEDICINE

Number One

ENDOCRINE STUDIES

BOSTON
1929

THIS GROUP
of
COLLECTED STUDIES
from
THE ROBERT DAWSON EVANS MEMORIAL
is dedicated to
the living memory of
MARIA ANTOINETTE EVANS
the Founder

1929

FOREWORD

The papers collected in this volume are the first formal presentation of the results of investigations begun in 1912. During the seventeen years that have elapsed, these studies have formed one of the major activities of the institution. In their course between four and five thousand individuals have been carefully studied, the program involving both extended clinical observations and detailed laboratory measurements. A large part of the Staff have either been chiefly concerned with these investigations or have contributed materially toward their prosecution. The work in its present embodiment is the outcome of true coöperative effort, and each of the group has made a personal contribution which finds expression in the following pages.

Through the generosity of the Trustees of the institution these papers have been collected and are offered to their colleagues by

THE STAFF.

STUDIES OF THE ENDOCRINE GLANDS.

I. A GENERAL METHOD FOR THE DIAGNOSIS OF ABNORMAL FUNCTION

ALLAN WINTER ROWE, Ph. D.

From the Evans Memorial
No. 109—A-57

BOSTON

This paper is the first of a series summarizing the results of a study on the diagnosis of endocrine diseases by objective methods. The work was begun in 1912 and in its course nearly 3,000 individuals have been carefully studied by a large group of clinicians and laboratory workers.

During the past few years several brief papers have appeared (1) presenting certain preliminary statements on the results of these studies. These have been supplemented by the reports of several clinical investigations based upon the method (2). With the completion of a series of 1,000 cases in which this procedure has been applied,* it has seemed desirable to present the facts thus far elicited with such conclusions as they may be felt to warrant. The present paper, as the title implies, deals with the general technique. Subsequent papers will present the details of the characteristic pictures of each of the several established endocrine entities. Finally, special treatment will be accorded those conditions which simulate endocrine disease and are frequently erroneously ascribed to it, but which can be shown by objective study to result from disease states not associated with the ductless glands.

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* Since beginning the compilation of the data here presented, over 2000 additional cases have been studied. The findings in the second group confirm and amplify, in a most gratifying manner, the conclusions drawn from the first.

The science of endocrinology, if so ambitious a designation be warranted, constitutes one of the newer chapters in medical history, and one that is still in the writing. True, the general concept of an internal secretory activity was first offered many centuries ago, but in this earlier form it derived solely from uncontrolled speculation and not from observation and experiment. First in the 19th century did certain definite, well-described clinical entities come into being in which an endocrine etiology was recognized by the individual authors whose names these syndromes bear, and toward the end of this period active glandular extracts were prepared and therapeutically applied. Finally, at the very beginning of the present century, Abel and others isolated the first active principle in a pure state.

These investigations, of which this paper is the first formal statement of results, are the expression of an effort to establish a series of objective criteria both for the general identification of disturbed endocrine function, and particularly for the determination of the individual gland involved. The field of so-called vital function testing has offered rich possibilities both by standardizing tests already described and by formulating new procedures when such were needed.

In the main, vital function tests have been designed to indicate an individual departure from the normal and have sought a marked degree of specificity. With the highly complex control of individual bodily functions, it has followed naturally that the reporting of each new test has been a signal for the recording of sweeping exceptions of both a positive and negative character. By questioning the specific character of the test its results have lost authority, and this in turn has frequently discouraged further study and application. Such an outcome is unfortunate and unwarranted. The level of any body function is certainly controlled by a large number of interrelated agencies which are mutually dependent and highly sensitive to changes in any one of them. The disturbance of any one equilibrium produces changes in the balance of a number of other related control factors and may produce end results of a really significant character. As a vital function test can, at best, only record end results, a lack of complete specificity is confidently to be predicted. Even the highly differentiated tests in the field of serology fail to fulfill their purpose completely.

From another standpoint, however, this very multiplicity of control factors offers the largest element of value. The selection of a series of function tests gives not a single criterion of a single disturbed function, but a series of interrelated criteria in each of which several functional activities are involved. Thus while several factors influence the magnitude and direction of the result of each observation, it seems highly improbable that all of a series of widely divergent tests should be uniformly affected both in quality and amount by each of the several agents involved. The accuracy of this assumption has been amply verified in the series of cases reported in these papers. In passing, the writer wishes to state that no novelty is claimed for the majority of the tests, as such. It is chiefly in the angle of approach that the present method differs from others.

A point that cannot be over emphasized is the necessity for quantitative measurements. Differences as observed in many instances must be of degree and not of kind. Only the most exact methods available are suitable for this purpose and these should be as rigorously quantitative as possible.

The investigation has naturally divided itself into three phases. In the beginning, groups of apparently normal individuals were subjected to a long series of tests and observations under carefully controlled conditions, and the individual level of performance exactly recorded. Tests were retained or discarded as they served or failed to define standards of normality within reasonable limits of variation.

The second phase of the study called for the application of the same series of measurements to individuals in whom there existed clear-cut involvement of single glands. To this group belong male and female castrates and thyroid and pituitary patients after ablation operations. In addition, a few progessing cases of exophthalmic goiter and of acromegaly were studied with just recognition of the uncertainty of their true etiology. The impossibility of establishing adrenal failure in man by surgical means limited the inclusion of this gland to the rare case of Addison's disease, in which the probable underlying pathology possibly later could be established by necropsy. The very small number of such cases which have been studied prevents that clear-cut definition which the other principal glands possess. The application of the tests to this entire group indicated both the directions and magnitudes of departure from the several base lines, and also established certain norms which were equally significant for the purposes of differential diagnosis.

These standards of performance indicate trends in functional change, the absolute magnitudes being conditioned by the severity of the disease and such intrinsic variables as age, sex, and similar biological factors. The influence of these latter makes it essential, where possible, to express results in relative terms, rather than those of the absolute data from which the relationships derive. For example, basal rates are profoundly influenced by both age and sex, as well as by such other standard measurements (height, area, etc.) as have been selected for correlation purposes. In like manner, the galactose tolerance of the normal female varies throughout the life span, apparently being regulated by the level of sexual activity; the normal male, on the other hand, presents an unvarying level from birth to death. With standards which are themselves variable through biological change, relative values are necessary for any basis of comparison.

In the collation of data certain other factors must receive due and constant consideration. For purposes of clarity, certain terms must be defined in order that in later use they may possess a constant meaning.

The term "hypofunction" is applied to that condition in which all of the clinical and laboratory findings indicate a lowered functional level—the extreme picture of which is produced by complete ablation of the gland—in other words, a state of demonstrable diminution or lack of internal secretory activity.

"Hyperfunction" is used to indicate a condition in which all measurable function levels are of opposite sign to those produced by ablation.

"Dysfunctional" states are those in which evidences of hyper- and hypo-activity are simultaneously observed. Such conditions arise, for example, when endocrine organs initially hyperactive are undergoing a functional involution to an ultimate hypoactive state. Years ago Cushing (3) called attention to such involutions in acromegaly, and the writer and his associates have frequently observed analogous conditions in thyroid disease. When such involutions occur, all the functions influenced by the gland at fault are not affected at the same rate of speed, and a variety of intermediate pictures is seen, depending upon the degree of the involution at the time of observation.

A second factor in the production of dysfunction lies in the plurality of certain of the endocrine structures. The adrenal, the adult ovary, and the pituitary, all embody certainly two functionally independent tissues, and with the last named yet other possibilities exist. Further, the single gland may produce more than one active principle as the result of its endocrine activities. These several variables naturally can produce a number of intermediate dysfunctional states. With the two extreme functional pictures properly defined, however, these intermediate conditions may be capable of at least a partial analysis.

The third and last phase of the investigation has been the study of the level of function of the individual case. After the careful elimination of all non-endocrine disease conditions which might produce the observed deviations from the norm, the data have been interpreted to define a tentative endocrine diagnosis. Finally, the indicated corrective measures have been applied, under careful clinical control and with repeated laboratory tests, to that gland which has been shown probably to be at fault.

Certain points in the foregoing require brief exposition for the sake of emphasis.

First, no single test can be regarded as significant unless it be checked and controlled by a number of other independent observations. For example, the diagnosis of thyroid disease on the basis of the basal metabolic rate alone is wholly unwarranted. Such a practice could lead to the performance of a thyroidectomy in a case of leukaemia, and certainly has caused the administration of vast quantities of thyroid preparations to individuals with normal thyroid glands.

Second, no single finding suggestive of an endocrine disease should be adduced to support such a diagnosis until all possible non-endocrine causes of the phenomenon have been ruled out by observation and test. For example, a slight eosinophilia is found in pituitary disease, but should be regarded as signifying such a condition only after the elimination of acute infections, protein sensitivity, skin eruptions, and intestinal parasites—to name but a few among the many. Over-enthusiasm in the interpretation of tests to support an endocrine diagnosis may well lead to the failure to recognize the true underlying cause of the patient's disability.

Third, in the study of each case, careful clinical observation is as important as are laboratory tests. The latter furnish a basis of tested fact for the interpretation of the subjective evidences of the former. But equally, medical history and physical examination offer data which may definitely establish the diagnosis, the laboratory findings serving chiefly as confirmatory supporting evidence. Both are essential, the one complementing and supplementing the other, with the diagnosis resulting from a judicious combination of the factors of each.

One other matter may be briefly considered. In the following pages results will be given from cases exhibiting disease of the pituitary, the thyroids, the gonads, and the adrenals. The pancreas has been omitted since the determination of diabetes—and the writer is in accord with Allen (4) in the limitation of this term to the syndrome caused by failure of the islands of Langerhans—does not usually require so elaborate a procedure as that to be described. The parathyroids have also been omitted because but little is known concerning the disease picture produced by disturbance of their function. On the one hand, several different causes may produce a low blood calcium, and on the other, the correlation of certain disease states with parathyroid inadequacy rests solely on unchecked speculation. In a recent treatise on these glands, Vines (5) reviews a series of conditions said by some to be benefited by parathyroid therapy that would place this product in successful competition with any of the six best sellers of proprietary origin.

A few glandular structures, such as the pineal, thymus, and spleen, are to be regarded as on the borderline, their place in the endocrine family by no means firmly established. Yet other tissues seemingly enjoy their endocrine status through the brevet conferred upon them by the manufacturers of pharmaceutical preparations.

The pluriglandular group, discussed in the later pages, is made up almost without exception of cases in which surgical intervention in one endocrine gland is superimposed upon functional aberration in another. In a series of nearly 3,000 cases the writer has seen but two or three in which there has been apparently a coexistent primary disturbance in more than one endocrine gland. With this truly insignificant proportion, common sense would ascribe the failure to define a single primary focus rather to the lack of knowledge of the observer than to the existence of the conventional pluriglandular syndrome. This statement is not intended to deny the possible existence of a true pluriglandular state, but only to emphasize the essential rarity of such a condition. True, the endocrine glands are among the powerful regulators of the general body metabolism, and failure of any one of them engenders functional derangement in other endocrine and non-endocrine tissues alike. This relationship is one of sequence and does not determine a pluriglandular syndrome in the conventional sense. Further, treatment solely of the primary focus—and if the secondary changes be in a reversible phase—if successful, corrects these latter as a result of normalizing the gland initially at fault. A pertinent illustration is the amenorrhoea of pituitary or thyroid origin.

In the latter discussion, the pituitary and thyroid cases are classified as ''hyper-'', ''hypo-'', and ''dys-functional,'' in accordance with the definitions discussed above. The gonad cases are all classed as ''hypo-functional,'' and to this exception may be taken. The writer has never seen a case of hyper-gonadism, *i. e.,* one presenting a picture the opposite of that produced by castration. The diagnosis of hypergonadism in cases referred for study is usually found to be based upon a record of a libido in excess of the observer's concept of the normal. Failing one terminal phase, an intermediate dysfunctional state is hard to define. For this reason, the writer has adopted the simplified classification, recognizing the limitation of its use. For similar reasons, the adrenal cases are also grouped in the single category. There is perhaps even less warrant for this, but if it errs, it is on the side of conservatism.

As the work was first outlined and undertaken, the subjects were admitted to the hospital for a period of seven days, and were thus under control for the duration of the study. The results of certain tests presuppose an adequate nutritional level, and consequently a diet was outlined to meet this requirement.

As these investigations were not intended to be exact metabolism studies in the sense, for example, of a nitrogen balance measurement, every effort was made to render the diet as varied and palatable as possible. As no exact analysis of the food intake was required, values as computed from Locke's compilation (6) were sufficiently accurate for the purpose. As the writer has elsewhere emphasized (7), such elastic regulation of the diet is of importance in experiments of any duration. The average individual, indifferent alike to the urge of pure science and the enthusiasm of the dietary propagandist, is influenced unfavorably, both directly and indirectly, by the continuance of an unvaried and potentially unpalatable diet. Diets were designed to give at least 6 grams of carbohydrate, 1.5 grams of protein, and a gross energy content of 45 calories per kilogram of body weight. Patients have been permitted to exercise a large degree of freedom in relation to their diet, and in the later studies it has been found necessary only to insure a protein intake above a maintenance level and a carbohydrate allowance sufficient to prevent depletion of the glycogen reserve. In general, the ordinary hospital fare, as outlined by a competent dietician, has been found entirely satisfactory. In isolated cases patients are under special dietary regimen at the time of reference, and this is continued during the hospital stay. For those preferring it, lunch is served at noon and the heavy meal at night. Regulation is secured in the amounts served, not in limitation of the variety.

In connection with the liberal dietary provision, every effort has been made to have the patient's hospital stay depart as little as possible from a normal regimen. Schedules, to be discussed later, are drawn to allow for free hours, and patients are encouraged to go out, see friends, and indulge in reasonable recreation, including theater attendance and other evening diversions. This serves the purpose of minimizing the irksomeness of an enforced hospital stay and, most importantly, produces a state of mind which makes for a maximum of co-operation. In the writer's opinion, this provision should be stressed, as certain of the tests are undoubtedly influenced by the patient's mental state. The more nearly the patients' lives in the hospital compare with their daily habit, so more nearly are the conditions reproduced under which they have experienced their individual symptoms.

As was intimated above, to conserve the patients' time and yet to permit thorough study, a definite schedule has been drawn up which outlines the sequence of certain basic routine procedures and allows opportunity for the inclusion of a wide variety of special examinations. These latter are selected on the basis of the suggestions developed in the routine examination. Patients are received only on Saturday afternoons, and under ordinary circumstances are discharged one week later. Where certain procedures are found to be necessary which are time consuming and do not permit the simultaneous performance of the routine tests [gastro-intestinal x-ray series, Graham test, duodenal function (McClure), and similar observations], the patient is held over for such additional days as are required. Routine tests are performed in duplicate or even repeatedly, if first results are uncertain. The general form is shown in Table I. It is understood that selections are made from the special examination group to conform with the needs of the individual patient.

TABLE I

GENERAL SCHEDULE ("Long Form")

	ROUTINE PROGRAM		SPECIAL EXAMINATIONS
First Day (Sunday)		A. M.	
7:00	Start collection Urine I.		
7:30	Blood I. Complete Morphology.		
7:35	Breakfast. Diet begins (1).		
9:30	Physical Examination.		
		P.M.	
	History.		
Second Day		A. M.	Sputum Collection.
7:00	Complete Urine I.		Special Liver Function.
10:00 12:00	Phenol Sulphone Phthalein.		Electrocardiogram. Endermal Tests.
		P. M.	
12:30	Lunch. Salol I.		Psychometric Examin't'ns
2:30	Adrenalin Mydriasis.		Psychiatric "
4:00	Alveolar CO_2 I. Blood Pressure.		Neurological " X-Ray (general).

Third Day A. M.
7:00 Start collection Urine II.
8:00 Basal Metabolism.
Vital Capacity.
Alveolar CO_2 II.
9:30 Breakfast.

Respiratory Quotient.
Faeces Collection (2).
Physical Measurements.
Surgical Examinations.
Pelvic "
Otological "

P. M.

Neuro-Otological Exams.
Ophthalmological "
Audiogram.
Photographs.
X-Ray (general).

Fourth Day A. M.
7:00 Complete Urine II.
8:00 Basal Metabolism.
Spirometer Measurements.
9:30 Breakfast.
10:00 Phenol Sulphone Phthalein.
12:00

Gastric Function.
Pneumograph Records.
Electrocardiogram.
Polygraph Record.
Cystoscopic Examinations.
Cardiac "
Chest "
X-Ray Pyelograms.

P. M.
Repeat second day.

Neurological (Electrical) Examination.
Audiogram.

Fifth Day A. M.
5:00 Start Collection Urine G-1.
6:45 Blood II (3).
7:00 Complete Urine G-1, Start G-2.
Test Meal of Galactose I (20 grams).
(+15 gms. Urea in 200 cc. H_2O) (4).
9:00 (5) Complete Urine G-2. Start G-3.
11:00 (5) Complete Urine G-3. Start G-4 (4).
Breakfast.

Dental Examinations.
Laryngological "
Ophthalmological "
Certain special Examinations of morning of 4th day.
6:45 Blood III for Blood Sugar Curve.
9:00
(Stool) (2).

P. M.
1:00 (Complete Urine G-4)

Lumbar Puncture.
Special Examinations.
(Phychological.)
(Psychiatric.)

Sixth Day A. M.
5:00 Start Collection Urine G-1a.
7:00 Complete Urine G-1a. Start G-2a.
Test Meal of 5th day (7) ± 10 or 20 gms.
Galactose (10-20% solution).
9:00 (5) Complete Urine G-2a. Start G-3a.
11:00 (5) Complete Urine G-3a.
Breakfast.

6:45 Blood Chemistry II.
Urea Index (R. W.).
Stool (2).
Chest Examination.

P. M.

Lumbar Puncture.
Special Renal Tests.

Seventh Day A. M.

Repeat 6th Day Schedule, changing Galactose Test Meal of 6th day (7) ±5 to 20 gms. Collecting Urines G-1b, 2b, 3b.

11:00 Test ends

or

Omit 3rd Galactose Test and start Gastro-duodenal Function Test (McClure).
Or, Gastro-Intestinal X-Ray Series (6).
Or Graham Test (6).
Or Start Mosenthal Diet for Kidney Function.

P. M.

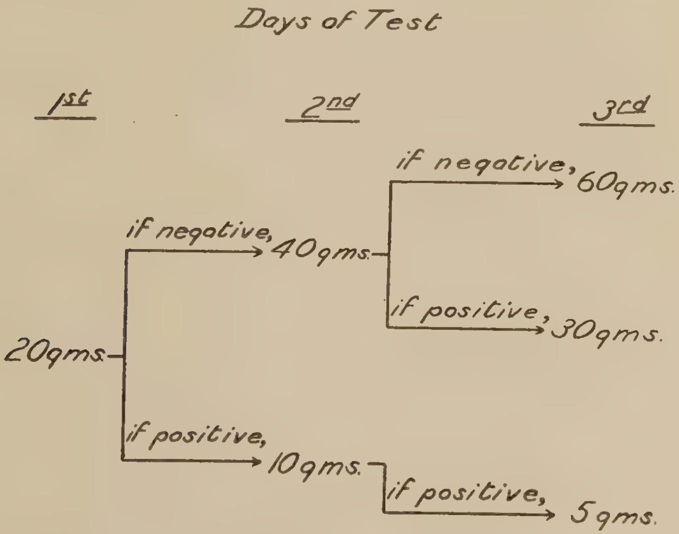
Repeat Phenol, Sulphone, Phthalein.

Eighth Day A. M.

Complete Galactose III or Gastro-Intestinal X-Ray Series (6), or Graham Test (6), or perform Mosenthal Test.

(1) Unless otherwise noted, meals are served at 7:30 a. m. and 12:30 and 5:30 p. m., respectively.
(2) If for blood examination, postponed and diet suitably modified before collection.
(3) Diet of preceding day is creatinin free.
(4) Included only when kidney function is desired.
(5) Patient remains in bed until 9:00 or better 11:00 a. m.
(6) If both Graham and G. I. Series desired, the former is done first and patient remains in hospital until completion of second.

(7) Galactose Chart, q. v.



The scope of certain of the examinations listed above is given in the next table.

TABLE I-a

Urine—I and II	G-1, 2, 3, 4; G-1a, 1b, 1c; 2a, 2b, 2c	
Complete Routine	Sugar	Sugar
Nitrogen Partition	Urea	
Microscopy of Sediment		
"Urobilinogen"		
Special test as indicated		

Blood—I	II	III
Morphology	Morphology	Sugar
	Serology	Urea
	Chemistry	
	N. P. N.	
	Urea	
	Uric Acid	
	Creatinin	
	Sugar	
	Special tests as indicated	

While the method of study outlined above gives a large amount of correlated information, it is time consuming, and moreover, the enforced hospital stay is a definitely limiting condition. Further, the underlying etiology in a number of cases can be determined with a much less elaborate and detailed examination. To meet this need, an abridged schedule has been outlined, embodying certain essential features of the longer study, and this "short form" has proven most helpful in the resolution of diagnoses. The essential features are given in the next table.

TABLE II
Abridged Schedule ("Short Form")

The patient reports at the hospital at 8 a. m. (or somewhat earlier) in a fasting state, and bringing the full 24-hour collection of the urine completed on that morning. After a suitable period of rest, the following schedule is carried out:

8:00 A. M. Basal Metabolism (first measurement at 8:30 or later).
Vital Capacity Measurements.
Alveolar Carbon Dioxide.

9:00 A. M. Injection of Phenolsulphonephthalein.
Physical Examination.
Medical History.

10:00 A. M. First P-S-P Collection.
Blood taken for
    (a) Morphology
    (b) Chemistry
    (c) Serology.

11:00 A. M. Second P-S-P Collection
Special Examinations and Consultations.

1:00 p. m. Patient discharged.

A light breakfast may be served after the blood specimens have been taken. By systematic arrangement several special observations and consultations, as suggested by the history and physical examination, can be performed on the morning of the test. If many observations are required, or if lengthy operations such as x-ray studies of the gastrointestinal tract or the duodenal function are required, return on a later day may be necessary. The sugar test can be carried out at home, each set of samples being sent at once to the hospital for analysis and the next dose of sugar, as indicated by the latter, sent back to the patient.

The degree of definition obtainable by the two procedures is interesting. Under present conditions, less than 3 per cent of the patients undergoing the week's study (''Long Form'') are discharged as unclassified, and many of these are partly resolved. For example, five patients in this group giving data indicative of either pituitary disease or of neuro-syphilis refused the lumbar puncture, which would probably have resolved the question. Similar conditions would account for several of the remainder.

On the other hand, in a recent series of 500 patients receiving the morning study, 153 were reported at first as unclassified, and certain additional tests were requested. In 91 of these cases further study established the diagnosis. The greater part of the remaining 62 would undoubtedly have been resolved had the requested supplementary information been forthcoming.

In considering the results obtained in this series of 1,000 cases, certain facts must be borne in mind. With the large number of data involved in the evaluation of each case, a statistical method of presentation is imperative. As, however, each diagnosis rests upon the interrelationship of the many individual facts recorded, such a general compilation in some measure defeats its own end and tends to obscure the real findings. To illustrate: A nephritis coexisting with an ovarian failure may cause a rise in blood uric acid not characteristic of the latter condition and suggesting pituitary disease, in which such an increase is really significant. In certain dysfunctional conditions the blood may be strikingly lymphoid or leucoid, depending on the type and phase of the dysfunction. In any summary these opposing conditions tend to compensate each other and mask the really significant divergences. By judicious selection, a group of extreme hypo- and hyper-functional thyroid cases could be assembled in which the algebraic sum of the basal rate deviations could be ±0. On the other hand, due allowance for all the factors operating entails so great a complexity in presentation as to produce an equal obscurity.

Another unavoidable and hampering condition lies in the fact that in a given group departures from the normal reflect in large degree the severity of the condition. The inclusion of a number of incipient and mild cases tends to minimize the positive definition of a trend which will be strikingly shown by the individual advanced case. In the subsequent papers in which individual glands only will be discussed, these objections are partly met by greater detail in presentation; even so, they cannot be eliminated, and in the present paper they operate in full force.

With due recognition of the unavoidable limitations of the method of presentation, the data may be discussed in detail.

As was stated earlier, the present paper aims only to present the general method with such supporting data as may be recorded in significant form. Many informative details must be reserved for the subsequent papers.

HISTORY

Under this caption will be considered only those points which may assume significance for the diagnosis of endocrine disease. At the risk of redundancy, the writer wishes to reiterate that there is no one of these points that may not equally be the result of some non-endocrine disease. Their incidence, however, is of sufficient frequency to suggest possible endocrine disorder. That all episodes should be dated to establish chronological sequence, should not require comment.

(a) A family history of established endocrine disease is of interest. There seems to be what may best be described as a ''constitutional tendency'' for the recurrence of endocrinopathies in a given familial line. Many such are recorded in the literature, and there are several striking examples in the writer's own experience. (See Family ''C,'' in the later Thyroid paper.)*

(b) The patient's own past history is most significant. Many endocrine conditions seem to date from severe infections. At the present time the number of individuals who seemingly exhibit sequelae of the severe influenza of 1918 and 1919 is striking. Earlier history of jaundice may help to clarify an anomalous sugar tolerance in thyroid failure. Trauma is always suggestive if involving an area associated with an endocrine gland. Rapid changes in weight, periods of over- or undergrowth, modification in facial contour or increase in size of hands or feet, loss or overgrowth of facial and body hair, are all possibly significant. The foregoing serve merely as illustrations. Many other suggestive evidences will be found in a well compiled history, and the reader can supplement any list as his own experience warrants.

(c) Headache is a frequent finding in this group of disorders, and seemingly confined to no one of them.

(d) Progressive deafness, without demonstrable anatomical change, has been shown by Drury (8) to be associated with endocrine disease in some two-thirds of the cases studied.

(e) A fatigability wholly disproportionate to recorded mental or physical exertion seems to be a cardinal point in the endocrine picture. One hesitates to crystallize this into a formula, but in the main there is a low level of vigor on arising, an improvement to some apex as the day progresses, and then a rapid decline to a level equal to or even below that of starting. Adrenal deficiency is an exception in that rest determines the high levels and exercise their rapid subsidence.

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* Recognition of this tendency does not imply subscription to the genial views of those writers who resolve all ethnic traits into manifestations of individual endocrine dominance. While such speculations are diverting, the exclusion of demonstrably powerful biologic forces, the complete absence of any objective supporting evidence, and the resolute elimination of all contradictory evidence, render them unconvincing.

(f) Gastrointestinal disturbances are frequently encountered. Ptosis, poor appetite, and constipation characterize the hypofunctional states, while the converse may obtain with hyperfunction of the pituitary, and especially the thyroid. Polydipsia and polyphagia are conventionally referred to pituitary disorders, but they may be found in both thyroid and, less frequently, ovarian cases.

(g) Unexplained pain in the lumbar region is frequently found in hypothyroid cases.

(h) The menstrual function is peculiarly susceptible to endocrine influences. Late onset of the catamenia, irregularity, scanty or profuse flow, and amenorrhoea and early menopause, are all features of endocrine disturbance. In pituitary and ovarian disease, the tendency is seemingly toward increase in the interspace with scanty flow; with the thyroid, the latter may be profuse and the rhythm increased or diminished.

(i) Sterility. For some time past the author and his associates have been carrying out elaborate studies on the numerous factors concerned in failure of reproduction. Among these, endocrine disorders take an important place, both by the determination of anatomic impedences as the result of abberrant growth, and also through functional disturbances which influence the viability of the sex cells. In this later series, the pituitary, thyroid, and gonad are apparently operative in the order named. A history of miscarriages, with chronological detail, is of primary importance.

(j) Nervous instability and irritability are again among the most common findings. Without seeking a definition which is phantastic, it may be said that the victims of ovarian failure frequently present an active, insistent egocentricity, testicular loss or failure leads to profound mental depression, and the intense nervousness of the hyperthyroid may also be found in the hypofunctional case or merge to a less aggressive selfishness that expresses itself in a sullen truculence. The pituitary patients seemingly more nearly approach the normal level of nervous balance.

(k) Speculation as to the etiology of psycho-neuroses and psychoses, in recent years, has been dominated by two schools of thought, one of which concedes only an endocrine cause, while the other with equal vigor abjures all but psychogenic backgrounds. Both theories are probably right in some measure. Certainly the writer has studied a few cases in which a frank psychosis co-existed with an equally demonstrable endocrine malfunction; in some of these both disorders were seemingly corrected by the indicated glandular treatment. Equally, other mental cases have shown a physical normality that eliminates any endocrine disease. It is as unwarranted to express all mental disease in an endocrine formula as to deny the influence of physical conditions on the state of mind. In a subsequent paper the writer will offer one or two striking cases illustrating each contention.

Aberrations of temperature response, such as hypo- and hyperthermia, are frequently found in thyroid disease and not unknown in other endocrine states.

The above constitute some of the suggestive points which may be derived from a well-ordered history. No attempt at completeness is possible within the scope of a journal article.

PHYSICAL EXAMINATION

Of necessity, this section deals chiefly with trophic evidences. A principal value of the physical examination is to indicate the existence of non-endocrine disorders to which the patient's disabilities may be ascribed. Only occasionally will the findings be positively suggestive of endocrine disease.

(a) The general body habitus, and particularly the relation of individual segments to each other or to the whole, are of real significance. Draper (9) has spent years in the study of such correlations and has gathered together a massive array of data which are most suggestive. It is to be regretted that others with the same fine enthusiasm lack the temperate reserve in interpretation that marks his concluding paragraphs (l. c., p. 222). Disproportion engendered by overgrowth before epiphyseal union has taken place or, equally, by premature closure, is highly suggestive in its measureable results.

(b) The localized distribution of obesity—as the girdle type found in pituitary disease, the fat body with thin legs of the patient with ovarian failure, and the generalized distribution in the hypothyroid individuals, really constitute a part of the foregoing. True, they are seldom realized in classic type, but they do define suggestive trends. The degree of obesity may make them all apparently merge in the thyroid type, as in a case of the writer's, a boy with pituitary failure who was less than five feet tall and weighed 400 pounds. Emaciation also may be suggestive where the loss has been selective.

(c) The amount and distribution of body hair with tendency to inversion in type of this secondary sex characteristic is significant. Each of the glands may produce one or more characteristic pictures.

(d) The spacing, development, and general appearance of the teeth should be carefully recorded. They may suggest disorders of the pituitary or thyroid or call attention to such conditions as rickets and congenital syphilis.

(e) The shape of the nose may be suggestive of an endocrinopathy. The characteristic forms in acromegaly and cretinism are illustrations.

(f) Marked asymmetry of the face and, less frequently, of other portions of the body, may suggest those growth anomalies resulting from metabolic derangement.

(g) The shape, appearance, and consistency of the finger nails undergo modification, particularly in thyroid disease.

(h) The general character of the skin and the presence of skin eruptions should always be noted. With even the meager knowledge of today, it seems possible that endocrine disease may engender certain trophic changes in the skin, possibly by indirect influence on the general metabolic level. Myxedema in thyroid failure is the prototype.

(i) A tendency toward the development of varicosities in the lower limbs has been noted in pituitary disease.

(j) Evidences of thyroid enlargement are as apt to be misleading as they are helpful. The diagnosis of thyroid disease on the unsupported evidence of a goiter has done and is doing grave mischief.

(k) Aberrations of vision can best be considered under a later caption, and this is true also of slow and rapid pulse rate, and changes of body temperature, blood pressure, and certain other physical measurements.

Again, in concluding this section, emphasis is laid on the illustrative character of the items selected, and even more strongly on the fact that they are never more than suggestive. Final diagnoses should not rest on the appearance of the eyebrow nor on an obesity deriving from what may be designated with courtesy as a good appetite.

Turning next to the laboratory findings and with reminder of the limitations imposed by tabular summation, the relative composition of the series may be considered.

TABLE III

DIAGNOSTIC SUMMARY

Diagnosis	Number of Cases		Per Cent	Group Per Cent
	Series B	Series S		
Not Endocrine	79	211	29.0	29.0
Pituitary, hypo- (−)	28	35	6.3	28.4
dys- (±)	113	103	21.6	
hyper- (+)	5	0	0.5	
Thyroid, hypo (−)	22	50	7.2	12.4
dys- (±)	14	21	3.5	
hyper- (+)	0	17	1.7	
Gonad, hypo- (−)	55	89	14.4	14.4
Adrenal, hypo- (−)	10	3	1.3	1.3
Pluriglandular, hypo- (−)	2	2	0.4	1.8
dys- (±)	6	8	1.4	
Unclassified, endocrine	6	63	6.9	12.7
doubtful	10	48	5.8	
Totals	350	650	100.0	

Too great significance should not be given to the relative magnitude of any group. The cases were all seen in a consulting diagnostic service, and in many instances the patients did not require elaborate studies to determine the underlying etiology; thus certain classes find but scant representation in this series. This is particularly true of the hyperthyroid group in which the presenting clinical picture, with its characteristic features, together with the history, physical examination, basal metabolism, and blood morphology, usually suffice to establish the diagnosis. At the most, the abridged study (Short Form) was adequate.*

The relative infrequency of demonstrable adrenal cases is strikingly shown. These represent the residua of a much larger group submitted in which bronzed diabetes or primary anaemia was found to be the true condition.

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* In a very few subsequent cases the longer study has been carried out. In all of these, non-endocrine diagnoses had been established elsewhere, and only complete investigations would permit a certain resolution of the question.

Considering the stress laid upon so-called pluriglandular syndromes, to say nothing of the widespread use of pluriglandular therapy, the figures here presented are worthy of remark. A further analysis of the eighteen cases offers yet more salient facts. These are presented in tabular form.

TABLE IV

ANALYSIS OF PLURIGLANDULAR CASES

Gland Involved	Surgical Cases	Total Cases
Pituitary	0	12
Thyroid	5*	11
Gonads	10*	12
Unknown	0	1†

SUMMARY

Etiology	No.	%
Surgical Cases	13	1.3
Doubtful†	1	0.1
Functional or organic	4	0.4
	—	—
Total	18	1.8

* Two patients had both ovaries and part of the thyroid removed.
† Mongolian idiocy.

Summarized, all but five of these cases derive their plural character from the interposition of surgery, and of these one, that of a Mongolian idiot, has only a conventional claim to inclusion; a second is a patient with thyroid failure in middle age who had seemingly an overactive anterior lobe in the prepuberal years. The whole question will be discussed in detail in a subsequent paper.

A few points, only, require comment. The designation of the degrees of activity of the several glands has already been discussed.

It is significant that in a series of 1,000 cases, in the main carefully selected as presenting evidences of probable endocrine disease, nearly one-third demonstrated a definite non-endocrine condition to which the presenting symptoms could be referred.* This fact emphasizes the unwisdom of the establishment of an endocrine diagnosis on purely clinical evidence alone, and, as a corollary, the necessity of eliminating disease condition unassociated with the ductless glands before interpreting data in terms of endocrine disease.

The incidence of pituitary cases seems to exceed either the thyroid or gonad by a ratio of 2 to 1. As has been pointed out, this is not strictly accurate as regards the thyroid, and the gonad figures are possibly influenced by the relative infrequency of male patients. As will be considered elsewhere (this article and a later paper on the gonads), the testicle in adult years, in contradistinction to the ovary, seemingly exercises but a meager influence on the general metabolic level. The individuals here presented were chiefly castrates, who have co-operated in the work, or were patients referred for sterility following a non-venereal disease. Within these limitations the figures as given possess a certain general significance. The predominance of the dysfunctional type of pituitary is interesting.

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* In the next 1,000 cases the non-endocrine percentage was 39.6. This was influenced in some measure by the study of certain special disease groups to ascertain if there were an endocrine element in their etiology. Deleting these cases, the remainder constitute about one-third of the whole.

The larger number of unclassified cases in the "Short Form" group illustrates the value of the additional tests. Had opportunity been given for further study, many of them could have been resolved, as has been pointed out above. More extended experience also tends to make the undetermined group smaller.

The next table presents some of the purely physical measurements and illustrates the wide range of the cases studied. As these are based on absolute values, they emphasize the worst features of collective presentation. All measurements are made on the nude subject and are determined with standard anthropometric equipment. Lung volumes are measured with a calibrated water-sealed spirometer of standard type.

The numerical preponderance of the female in the endocrine group contrasts with the relatively greater equality in the non-endocrine. In the main this agrees with other records, only the pituitary proving an exception. While the tallest case is in the pituitary group, the average corresponds to that of the entire series and is less than that of the non-endocrine section. The relative average age shows that this is not referable to an undue proportion of children. The age averages are in substantial agreement with the observations of others. The slightly greater age of the pluriglandular group reflects probably the time factor in the causation of the surgical element to which they are referable. The sitting height indices show a very definite uniformity. They are influenced by the female preponderance in absolute magnitude, and striking individual departures are lost in the summary. The failure of the gonad (and the pituitary) group to show a low value is due presumably to the fact that cases presenting disease in adult years dominate the series. In the

TABLE V

PHYSICAL MEASUREMENTS

Observation		Unit	Endocrine Group							Not End.
			Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	Total	
Sex	Male	%	37	22	5	23	0	16	24	42
	Female	%	63	78	95	77	100	84	76	58
Age	High	years	70	74	63	62	63	61	74	78
	Low	years	6	8	13	7	17	7	6	9
	Average	years	33	37	33	35	41	32	33	38
Height	High	cm.	195	184.5	174	177	188	181.5	195	193
	Low	cm.	103	131.5	148	115	146	113	103	139
	Average	cm.	164	162	162	162	166	160	163	165
*Sitting Height	High	cm.	100	96	94	96	95	92.5	100	99
	Low	cm.	56	75	77.5	64	80.5	62	56	72.5
	Average	cm.	87	86	86	85	88	85	86	87
Sitting Height Index			0.530	0.531	0.531	0.524	0.530	0.531	0.530	0.527
Chect	High	cm.	150	107	121	107	110	111.5	150	125
	Low	cm.	54.5	62.5	60	56	63	50	50	59
	Average	cm.	81	80	78	73	83	79	80	80
Weight	High	kgm.	164.1	124.5	124.0	89.0	128.0	113.0	164.1	145.0
	Low	kgm.	15.7	31.3	35.8	22.0	41.2	15.6	15.6	28.1
	Average	kgm.	67.4	61.8	62.0	52.6	70.0	62.9	64.4	61.5
Area	Average	sq. m.	1.73	1.66	1.66	1.55	1.78	1.66	1.69	1.67
†Lung Volume	High	c. c.	6200	4640	4940	4100	3200	4520	6200	5500
	Low	c. c.	600	820	930	1700	1140	800	600	300
	Average	c. c.	2960	2550	2710	2460	2440	2550	2760	3020

*Designated as "Trunk" by Dreyer. †Designated as "Vital Capacity" by Dreyer.

weight averages, the pituitary and pluriglandular groups (in the latter a pituitary influence is dominant) are well above the mean, while the emaciation of the adrenal cases is equally clearly defined. All of the endocrine cases save the pituitary, show values for the lung volume significantly below the non-endocrine group. Absolute values here are influenced by several extraneous factors which do not appear. The seeming diminution is in part apparent rather than real (see adrenal cases in next table), and in the main is probably due to the asthenia which is a characteristic of endocrine disease in general. As was stated above, in many cases absolute average values are not greatly informing; relative quantities tend to place greater emphasis on significant differences. In the next table are collated values derived from the Dreyer (10) and West (11) comparisons. With the former, only those correlations based upon sitting height ("trunk") are considered, as the author's formulation presupposes a relatively normal configuration, and in cases of obesity leads to impossible extrapolations. Further, but one occupational standard instead of Dreyer's three has been used, as by so doing disturbing com-

TABLE VI
"VITAL CAPACITY" COMPARISONS

Observation	Endocrine							Not End.
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	Total	
Weight—								
High	+247%	+ 82%	+107%	+ 19%	+ 78%	+ 67%	+247%	+ 75%
Low	− 42%	− 29%	− 37%	− 36%	− 14%	− 36%	− 42%	− 35%
% above normal	62	57	55	25	65	55	58	48
Average	+ 29%	+ 23%	+ 24%	+ 16%	+ 24%	+ 26%	+ 26%	+ 17%
% below normal	38	43	45	75	35	45	42	52
Average	− 12%	− 15%	− 11%	− 19%	− 9%	− 13%	− 13%	− 12%
Total average*	+ 13%	+ 8%	+ 9%	− 10%	+ 12%	+ 9%	+ 10%	+ 2%
Chest—								
High	+ 96%	+ 36%	+ 66%	+ 15%	+ 43%	+ 47%	+ 96%	+ 36%
Low	— 24%	— 23%	— 17%	— 17%	— 18%	— 13%	— 24%	— 23%
% above normal	64	53	47	25	75	60	57	58
Average	+ 12%	+ 12%	+ 13%	+ 12%	+ 16%	+ 14%	+ 13%	+ 9%
% below normal	36	47	53	75	25	40	43	42
Average	− 7%	− 7%	− 7%	− 10%	− 10%	− 7%	− 7%	− 7%
Total average*	+ 5%	+ 3%	+ 2%	− 5%	+ 10%	+ 5%	+ 4%	+ 2%
Lung Volume—								
High	+ 18%	+ 12%	+ 23%	± 0%	− 11%	+ 17%	+ 23%	+ 17%
Low	− 62%	− 75%	− 67%	− 29%	− 60%	− 58%	− 75%	− 89%
% above normal	11	9	10	8	0	6	10	17
Average	+ 6%	+ 7%	+ 7%	± 0%	− 0%	+ 12%	+ 7%	+ 5%
% below normal	89	91	90	92	100	94	90	83
Average	− 22%	− 28%	− 22%	− 19%	− 27%	− 24%	− 23%	− 26%
Total average*	− 19%	− 25%	− 20%	− 17%	− 27%	− 22%	− 21%	− 21%

*Weighted for number of cases.

plications are avoided. The whole matter has been discussed by the writer (12) in another place. Experience in this country shows that the "A" male and "B" female standards most nearly conform to average experience. In the West comparisons, for like reasons, only the male and female standards are used. In both series, children (boys and girls) are referred to the female standards, as experience has shown this to be most representative. The values presented in the table for Lung Volume ("vital capacity") are the averages of the Dreyer and West comparisons.

In the table above, "High" and "Low" represent the deviation from prediction in the two extreme cases in the group. The relative number of the group above and below prediction are indicated by percentages and the average deviation of each group is appropriately placed. The total average is the algebraic summation of the two groups suitably weighted for numbers. To illustrate, the heaviest pituitary case was 247 per cent above prediction (+), and the lightest 42 per cent below (—). Sixty-two per cent of the group were overweight, the average being 29 per cent above prediction (+), while the remaining 38 per cent were underweight, their average being 12 per cent below prediction (—). The whole pituitary group showed an average of 13 per cent above (+) prediction.

With the weight comparisons, the dominance of the pituitary and pluriglandular groups in part disappears, but the emaciation of the adrenal cases gains in emphasis. The chest values are indeterminate. The lung volumes in the total endocrine group exactly equal those in the non-endocrine. Of the individual components of the endocrine group, the thyroid and pluriglandular groups are most affected, the pituitary and, surprisingly, the adrenal* the least. The lowered lung capacity in the thyroid cases has already been commented on, and a number of years ago Bryson (13) called attention to the lessened chest expansion in thyroid disease. With the pluriglandular group it is possible that the low values reflect the influence of the twofold endocrine disorder which they present. Too great weight should not be placed upon lung capacity measurements, however, since the degree of co-operation of the subject influences the magnitude unduly. It is safe to say, nevertheless, that thyroid disease causes a diminution in this quantity that is of potential diagnostic significance.

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* The small number of cases composing this group makes this observation less significant than in the case of values for the other series.

The general examination of the urine offers numerous points of interest. Many of them cannot be reduced to presentation in tabular form, but certain significant measurements are grouped in the next table. Of the methods selected, that of Ehrlich (14) for the so-called "urobilinogen," the amylase method (15)* and the standard method for salol may be mentioned. The values for the "phthalein" test were obtained by comparisons with graded standards in a du Boscq colorimeter. The urea curve was determined by four two-hour collections following a test meal of 15 grams of pure urea taken in a fasting state and following a two-hour control collection. Folin's (16) method was used for the analyses.

TABLE VII.

URINE DATA

	Endocrine						Not
Observation	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	End.
Volume ....Av.	1230	1110	1130	1140	1440	1220	1260
Specific Gravity.Av.	1.019	1.019	1.019	1.016	1.016	1.019	1.018
Albumin, % positive	22	20	19	69	28	9	17
Casts, % positive	16	16	17	23	11	13	15
Sugar, % positive	24	12	27	23	33	16	10
"Urobilinogen" % positive	36	3	0	0	22	16	2
Amylase Index.Av.	18	16	16	13	18	11	14
Salol (minutes).Av.	74	91	88	96	90	61	79
Urea Curve, Normal	71%	80%	86%	28%	83%	..	80%
Low	29%	20%	14%	72%	17%	..	20%
P-S-P,** 2-hour Total Av........	50%	55%	54%	50%	53%	53%	53%

Considering first the urine volumes, it is evident that the pituitary does not exhibit any striking augmenting influence. Naturally, in the series a number of patients exhibited polyuria, but a compensating oliguria was shown by others. As the work of Camus and Roussy (17), Houssaye (18) and, most recently, Bourquin (19) has thrown some doubt on the unique influence of the pituitary as the direct causative agent in diabetes insipidus, this is rather to be expected. The lowering influence of thyroid and adrenal failure is here shown as a tendency. The low gonad value is in part ascribable to the overwhelming predominance of females coupled undoubtedly with a tendency to lessened elimination. Only the adrenal group shows a marked decrease of dissolved matter ("total solids"), though many individual cases of thyroid failure exhibit the same tendency. The healthy appetite of many of the thyroid subjects tends to mask the lowered metabolic level which undoubtedly exists in failure of this gland. It will be remembered that the hyperthyroid group in this study is too small to influence the summated results. While albuminuria is a frequent observation in the entire series, its dominance—and in less degree the incidence of casts—in the adrenal cases is a marked evidence of the nephritis, which is a usual feature of this condition. In general, however, in the endocrine cases, albumin and casts may be regarded rather as evidences of disturbed kidney metabolism than as indicating the existence of true nephritic states.* A striking observation is the relative frequency of glycosuria in the endocrine group. Overactivity of the posterior lobe of the pituitary (but not underactivity as recorded by several writers), hyper- and dys-functional states of the thyroid, and ovarian failure have frequently been recorded as causal conditions. The lower percentage in the thyroid group rests on the relatively lesser influence of this gland on carbohydrate metabolism. This will be considered later under "Sugar Tolerance." The writer's findings with adrenal failures are not in accord with the frequently expressed opinion that this condition raises sugar tolerance. Reference will be made to this point later, both in this and in a subsequent paper. Another interesting feature is the not infrequent appearance of glycosuria in the non-endocrine group. It is to be remembered that pancreatic cases were excluded from this compilation. The easy assumption, so frequently recorded, that glycosuria indicates an incipient diabetes (that of pregnancy, for example) is but a persistence of the erroneous concept of unitary control of body functions. Lesions of the central nervous system (without other evidence of indirect pituitary involvement), syphilis, liver disease, primary anaemia, leukaemia, and cancer, are all represented in the group here recorded. This question, too, will be discussed in detail in a later paper.

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* Later discontinued, as other methods of evaluating kidney function were found to be far more significant.

** Phenolsulphonephthalein.

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* In the subsequent paper on the thyroid, emphasis will be laid on the "pseudo-nephritis," which we have already recorded in this condition.

A positive "urobilinogen" test stands out definitely in the pituitary group or in those series such as the pluriglandular and "unclassified" in which this gland is or could be a factor. In the positive thyroid cases there was a concomitant liver dysfunction, while this latter condition and primary anaemia were responsible for its appearance in the few non-endocrine cases. When they can be excluded, the test offers one fact toward a pituitary diagnosis. The non-specificity of the test as an evidence of the presence of urobilinogen has already been touched upon.

The amylase test falls short of any real significance and in the later studies has been discontinued. Salol is a rough measure of gastric motility, if kidney function be demonstrated to be normal. It is included for its possible information in the sugar tolerance test. The lowered kidney permeability of the adrenal cases is also revealed in the urea curve. The observations of this laboratory would indicate that an inadequate level of protein metabolism may be a source of error in the results of this test. Whether through tissue absorption of urea or through some other agency, the fact remains that many patients with a partial protein inanition and demonstrably sound kidney function show a low curve of urea elimination under the stimulus of a provocative urea test meal. Blood urea measurements recorded elsewhere (20) indicate that this is not due to failure or delay of absorption. The observed fact is suggestive. The phenolsulphonephthalein values seem only to illustrate the relatively inconclusive character of this test in all but terminal phases of kidney involvement.

Another observation based upon the determination of urine constituents is found in the so-called "nitrogen partition." While under ordinary conditions urea constitutes the major portion of the protein waste, uric acid, creatinin, and ammonia are constantly present* in appreciable amounts, representing end phases of specialized metabolic processes. In addition, there is the undetermined fraction made up of a large number of both known and unknown nitrogen-containing compounds usually present in small amounts. It should be repeated that this test as performed in this study does not constitute a part of an elaborate nitrogen balance measurement. The first urine examined gives information both as to the daily dietary of the patient and the relative composition of the protein waste. When a second urine is tested—as in the routine of the Long Form—it gives the added information of the influence of the hospital standard dietary on the quantitative performance of the patient, and serves as a check on the first. In the first instance, the total gives valuable evidence on the accuracy of the patient's statement of dietary habit,* and in the second, as will be shown, the items of the partition may assume a diagnostic significance. Total nitrogen is determined by the standard modified macro-Kjehldahl method (using both copper and potassium sulphates), urea, uric acid, creatinin, and ammonia by the several procedures devised by Folin (22). The data are collected in the next table.

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* Exception is noted of the disappearance of the last named when the combining power of the plasma exceeds 80 volumes per cent. (See Fitz and Van Slyke.) (21).

TABLE VIII

NITROGEN PARTITION

	Endocrine							Not
Observation	Pit.	Thy.	Gon.	Adr.	Pl.Gl.	Uncl.	Tot.	End.
Tot. Nitrogen. (gms.)	9.57	8.34	8.94	7.46	8.97	9.32	..	9.26
Urea “ (%)	80.6	79.0	80.9	79.8	80.0	80.7	80.3	81.1
Uric Acid “ (%)	2.0	2.2	2.0	2.2	2.1	2.0	2.1	2.3
Ammonia “ (%)	3.9	4.2	3.9	4.7	4.9	3.6	4.0	3.8
Creatinin “ (%)	4.4	4.2	4.5	4.0	4.8	4.2	4.3	4.5
Residual “ (%)	9.1	10.4	8.7	9.3	8.2	9.5	9.3	8.3
Residual, total % of cases equal or over 9%	45	56	45	54	44	61	49	38

In the table given above, the first line records the average nitrogen elimination of the individuals composing each group, while the next five indicate the percentage distribution among the five components. The last line records that part of the group exhibiting a ''residual'' or ''undetermined'' fraction in excess of the conventional normal of 9 per cent. For example, 56 per cent of the thyroid cases showed residual fractions above the normal.

All of the total nitrogen values here presented are above the maintenance level and all of them are likewise below that which would correspond to the hospital allowance of protein. (Based on the protein allowance in terms of body weight, this would range approximately from 11 grams in the adrenal cases to 15 grams in the pluriglandular). The discrepancy becomes less when it is remembered that two-thirds of the patients collected their urines at home and that the first urine of the remainder was collected in such manner as to show the home nutritional level. A lowered level of protein metabolism in thyroid and pituitary failure has often been recorded, while the increase in hyperthyroidism is regarded as pathognomonic. The thyroid hypofunction effect is shown here, but an adrenal influence appears even more strikingly. Lowered kidney permeability and the several influences due to asthenia undoubtedly operate here. The pituitary shows the highest level of the several groups, bulimia being one probable factor, but the existence of a generally normal level of many functions in this particular condition being certainly another. In passing, it may be said that while the several types of pituitary disease cause certain strikingly significant departures from the normal, in a number of respects they conform straitly to conventional standards. The differential significance of this will be stressed later.

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* This ranges in experience from the obese lady who confesses to one egg and a biscuit or two a day, with 20 grams of nitrogen in the urine, to the equally subjective individual who claims a liberal dietary habit—and shows 3 grams. Body weight is not a safe criterion for estimating protein levels, and a partial inanition of this essential constituent influences significantly the basal rate, the blood chemistry, and other important magnitudes.

Turning to the several partition formulas, the only striking irregularity is found in the residual or undetermined moiety. Passing comment may be made on the constancy of the uric acid fraction, a constitutent which Falta (23) found to be increased in the pituitary cases, but which is not demonstrably influenced in this series.

The average value for the residual fraction in normal adults drawn from nearly 400 cases [Folin (24), Mathews (25), Long and Gephart (26), Rowe and Proctor (27)] is just under 6 per cent, with 10.9 grams as the average for the total nitrogen. Folin's original study demonstrated an increase in the relative amount of the residual nitrogen with lowered nitrogen elimination, but the percentage remains less than eight when the nitrogen elimination exceeds five grams. It is true that the residual fraction is determined by difference and so absorbs all of the errors incident to the other measurements, but these would operate equally in all groups large enough to nullify individual differences. Hence such variations as are actually observed must be significant even though the absolute magnitude may not be rigorously accurate. Further, the use of the best available methods by a group of technically skillful workers offers additional safeguard against gross error. The experience of the writer with several thousand such analyses has led to the adoption of the conventional value of 9 per cent as the upper normal level. Conceivably, this is slightly high, but the adoption of a somewhat lower criterion would serve only to emphasize the endocrine influence. As it is, the endocrine series shows an upward tendency most marked in the thyroid group, which also exhibits the largest percentage of individual cases exceeding the conventional normal limit.* The adrenal comes next and only the pluriglandular group shows an average less than the non-endocrine. Even here the percentage of individual cases showing high values is greater in the endocrine group. Further, the endocrine average is above, that of the non-endocrine group below, the conventional boundary. As the percentage of non-endocrine cases showing high residuals is not strikingly inferior to that of the endocrine group, however, a further analysis of the former is interesting.

Cases of leukaemia, malignant neoplasm, tuberculosis, and epilepsy show very high incidence and very high absolute values. Lower, but still significant, are primary focal infections, such as those of teeth and of tonsils, various lesions of the central nervous system, and primary anaemias.

The underlying mechanisms of this increase are still obscure. A study already reported in brief [Rowe and Proctor (27)], and shortly to appear in detail, demonstrates that while the amino-acid, hippuric acid and creatin fractions all show increase—the first, only, in significant absolute amount—there still remains an undetermined quantity which in the control (normal) group is 3 per cent, in the non-endocrine group about 5 per cent, and in the endocrine group exceeds 7 per cent of the total nitrogen elimination. Further, a determination of the neutral sulphur fraction (as possibly associated with nitrogen-containing molecules) shows no change of significant proportions. In other words, while known constituents of the urine, usually present in small amount, are found to be definitely increased, there remains a fraction of unknown composition still to be accounted for. This problem is now under investigation.

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* The unclassified cases are, for obvious reasons, omitted from this discussion.

As the urine constituents are derived from those of the blood stream, the chemical composition of the latter may next be considered. The routine examination calls for the determination of four nitrogenous constituents and of sugar. Individual cases call for additional observations, but in no series has any other single constituent been measured with sufficient frequency to warrant inclusion.

In the main, the methods outlined in the well-known Folin-Wu (28) procedure have been followed. Urea has been aerated rather than distilled, though both methods are used to control each other. The uric acid method has been varied in accordance with the suggestions later reported (29).

Neither the uric acid nor creatinin procedures are specific for the substances named, and this criticism is equally applicable to the sugar determinations. They all, however, give dependable and reproducible results, seemingly are not grossly in error, and the relative values thus obtained are to be regarded as significant. The collected data are given in Table IX.

TABLE IX

BLOOD CHEMISTRY (and Serology)

	Endocrine						Not
Observation	Pit.	Thy.	Gon.	Adr.	P. G.	Uncl.	End.
Non-Protein Nitrogen..mgm.	33	32	31	38	31	32	34
% over 35 mgm..........	29	26	20	58	25	24	26
Urea Nitrogen........mgm.	16	15	14	14	16	14	16
% over 17 mgm..........	17	20	19	18	19	10	24
Uric Acid.............mgm.	3.8	3.5	3.3	3.8	3.6	3.4	3.5
% = or over 4.0 mgm. (net)*	34	18	12	22	20	25	11
Creatinin ....mgm.	1.5	1.5	1.5	1.5	1.5	1.6	1.5
Residual Nitrogen.....mgm.	15.1	15.2	15.3	22.1	13.2	16.2	16.2
Sugar ....mgm.	94	98	97	84	96	95	97
% over 120 mgm.........	1	4	4	0	6	2	2
% under 80 mgm.........	5	5	8	50	12	8	5
+ Wassermann .....(cases)	0	1	0	0	1	0	10
+ Schwartz-McNeil .(cases)	1	0	0	0	0	0	0
+ Spinal Fluid......(cases)	1	0	0	0	0	0	2

*All demonstrated cases of nephritis deducted.

In largest measure the blood picture confirms the observations already made on the urine. Significant variation is shown by the high uric acid in pituitary disease. This is duplicated only in the adrenal group, and here are found other evidences of kidney disease which are lacking in the pituitary picture. The high residual fraction in the adrenal group is a striking observation possibly connected with the urine findings in these cases. No explanation for the low value in the pluriglandular group is at present known. The relatively greater frequency of high blood uric acid without demonstrable kidney disease lends to the datum a certain diagnostic significance. Hammett and his co-workers (30) observed this phenomenon in a small group of experiments with pituitary feeding. Whether it is due to an increase in uric acid or of some other substance giving the same reaction, remains to be ascertained.*

The hypoglycaemia of adrenal failure, frequently reported, is definitely confirmed in this series. That blood sugars are relatively normal in all of the other endocrine conditions renders this a point of significance for differential diagnosis.

The results of the serological examinations, included in this table for convenience, show nothing striking. The inclusion of the three positive cases in the endocrine group is reasonable, as the pituitary case with positive spinal fluid gave only a doubtful test, while the positive Wassermanns in the single thyroid and pluriglandular cases showed a possible lues superimposed upon unmistakable endocrine disease.

Relatively few reports of blood chemistry in endocrine disease are found in the literature, but the older art and science of blood counting has developed certain conventional formulas for the blood morphology. The lymphocytosis in thyroid, pituitary, and adrenal malfunctions, the eosinophile increase in the two latter, and the increase in large mononuclear cells in thyroid disease have been frequently recorded. Less certainly established are lowered haemoglobin in thyroid and pituitary failure, lowered red count in these and adrenal failure, and leucopenia in the first two. A prevailing high red count has been remarked in acromegaly. The results in this study are grouped in Table X.

No striking deviation in the haemoglobin content is exhibited by any of the groups. The primary anaemia cases were too few to influence the average in the non-endocrine group. The red count shows a surprising uniformity. Naturally, individual cases with well-marked secondary anaemia are absorbed in the

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* In a few observations by the modified Folin method (31), the uric acid amounts continued relatively high.

TABLE X

BLOOD MORPHOLOGY

	Endocrine						Not
Observation	Pit.	Thy.	Gon.	Adr.	Pl.Gl.	Uncl.	End.
Haemoglobin, %..........	89	87	90	87	91	90	88
Erythrocytes (1,000,000)...	5.11	4.92	4.98	4.79	5.09	4.95	4.93
Leucocytes (1,000)........	7.7	7.7	7.7	7.0	7.7	7.2	8.0
DIFFERENTIAL COUNT							
Polymorph. Neutrophiles, %	57	56	57	51	59	57	62
% = or over 75 %......	5	3	6	8	6	3	7
Lymphocytes	35	37	35	40	35	35	30
% = or over 33 %......	58	61	54	62	65	59	38
Eosinophiles	3	2	2	2	1	2	2
% = or over 3% (net)*.	30	25	21	39	6	17	14
Endothelial Leucocytes....	5	5	6	7	5	5	6
Abnormal Erythrocytes...	0.5%	2%	0	0	0	0	2%

average, but with so large a number the tendency toward relative normality would seem to be established. The leucocyte counts are a low normal, in every case somewhat below the non-endocrine group, and reaching possibly significant proportions only in the adrenal cases. The cases of leukaemia were omitted from consideration in deriving the leucocyte formula. An upward trend of the lymphocytes is unmistakable throughout the entire endocrine group, and is most marked in the pluriglandular fraction. Slightly over one-third of the non-endocrine cases show a lymphocytosis as against about 60% for the endocrine group. Pituitary disease seemingly tends to produce a mild eosinophilia, while two-fifths of the adrenal cases exhibit it. A like influence is somewhat less strongly shown in the thyroid section. Broadly speaking, the chief departures from the normal are a general trend toward lymphoid bloods and a slight eosinophilia more marked in pituitary and adrenal cases. As a matter of fact, the eosinophilia in pituitary disease is in our experience somewhat more striking than the tabulation would indicate. It suggests a tendency, however, rather than an established condition. The increase in lymphocytes in the non-endocrine cases shows certain well-marked etiological relations. Malignant neoplasms, tuberculosis, focal infections, syphilis, and the blood diseases, exhibit the condition in a significant percentage of the cases observed. As will be remembered, these are substantially the same conditions in which the interesting but non-specific high residual nitrogen fraction was manifested. In the endocrine group over 50 percent of the cases exhibit one or both of these anomalies, while nearly 40 percent of the non-endocrine fraction show the same deviation. The correlation of the incidence of these two abnormalities is interesting.

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* All cases showing acute inflammatory process, skin eruptions, protein sensitivity, and intestinal parasites, were omitted.

TABLE XI

CORRELATION OF HIGH RESIDUAL NITROGEN AND LYMPHOCYTES

DIAGNOSTIC GROUP	Residual Nitrogen Lymphocytes	Above Normal Normal	Normal Above Normal	Above Normal Above Normal
Endocrine				
Pituitary	(%)	17	30	28
Thyroid	(%)	21	26	36
Gonads	(%)	20	27	26
Adrenals	(%)	23	31	31
Pluriglandular	(%)	12	35	29
Total Endocrine*	(%)	19	30	30
Not Endocrine	(%)	25	25	13

Inspection of the table shows that in the endocrine group there is a relatively low incidence of high residual nitrogen alone. Patients showing lymphocytosis, and those in whom both appear are practically 50 percent more frequent in occurrence. The non-endocrine group exhibits an opposite relation as the coincidence of the two abnormal findings is but half of the incidence of each alone. We make no attempt at this time to explain the significance of this observation. The facts are reported as they occur. It may be permitted to comment, however, that on the basis of probability, cases showing both are about 2.5 times as likely to demonstrate an endocrine etiology."

During recent years the respiratory metabolism has played a most important part in the evaluation of endocrine conditions. The establishment of normal levels begun by Atwater and Benedict (32) and continued by the latter and his later associates, in a long series of fundamental contributions, has made possible the determination of the significant variations produced by disease. Studies of the influence of disease on oxygen consumption, practically initiated by Magnus Levy (33), but developed principally by Du Bois and his associates (34), have shown that deviations of the so-called basal metabolism may assume a most important diagnostic significance. The profound influence exercised by the various types of thyroid disease has somewhat overshadowed, in the minds of many, the definite influence exercised by other members of the endocrine group as well as by a variety of disease states unassociated with the ductless glands.

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* Unweighted averages. Weighting gives the practically identical values of 19-28-30.

** The unclassified cases, the great majority of which were probably endocrine, show the values 18-21-34. The endocrine element is here manifested as a tendency.

Two clinical methods are available for this measurement, both depending on the measurement of the gas exchange. In the open circuit procedure the expired gases are analyzed both for carbon dioxide and for oxygen and the energy exchange calculated from the oxygen consumption, with due allowance for the ratio of the two. In the closed circuit method, oxygen is rebreathed after removal of the expired carbon dioxide and the energy exchange calculated from the oxygen as measured, with the assumption of a constant (0.82) respiratory quotient.* Both methods number staunch supporters among the productive workers of this country and much polemical literature exists in which the relative merits of each are vigorously discussed. A review of this controversy can find no place in such a presentation as the present. We use the closed circuit method in our laboratories as the result of selection after long study of the problem. As in method, so in normal standards, two schools of practice exist.** Both take due cognizance of the variables of age and sex, but the Harris-Benedict formula (36) correlates with standing height and body weight, while the Aub-Du Bois equation (37) determines body area (calculated from the foregoing) as the third element of mutation. Again, the merits of each have been widely discussed. The practice of this laboratory is to compare the observed value with those predicted by each formula and report the mean as the probable deviation.

Before turning to the numerical data two points should be emphasized. First, all measurements are supposedly made on individuals in a basal state, i e., post-absorptive and both physically and mentally relaxed. Both methods are influenced equally by failure to observe these provisions and may easily present values which are definitely misleading. As all such errors tend to raise the observed basal rate, all measurements should be regarded as maxima with the true energy requirement of the patient equal to or less than that recorded, the degree of deviation depending upon the attendant circumstances. Second, the test should be applied under standard controlled conditions and a series of supplementary physical measurements such as pulse rate, temperature, and blood pressure, should always form a part of the laboratory record. The correlation of these data with the observed rate will frequently furnish evidence of the presence of vitiating conditions which might otherwise pass unnoticed. The conventional practice to allow for individual variation is to define the normal limits as ±10 percent from prediction. In view of the uniform tendency of error to augment the observed values we feel that —10 percent defines a definite hypofunctional trend, while equally we incline toward +15 percent as the preferable superior limit. In every case such conventional boundaries must never be regarded as sharply defined. In the interpretation of borderline basal rates, many concomitant observations must be taken into consideration; no single test in itself, except under most unusual conditions, is competent to establish a positive diagnosis. Its interpretation in the light of numerous other and independent records of fact lends a necessary authority not intrinsic in its own absolute magnitude. Finally, while the operation includes mechanical features, a machine-like freedom from error is far from implicit in the procedure. The sources of error are numerous and they can be held within reasonable limits only by intelligent and scrupulous care. The data for this series are given in Table XII.

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* The methods basing the calculation of the metabolic rate on the carbon dioxide output alone are so susceptible of error as to find no place in this discussion.

** Dreyer's (35) original suggestion of the use of body weight alone, offers no advantage, and the later generalization, based on calculated weight, is inapplicable to the clinical problem through the frequent departure of the patient from the arbitrary standards implicit therein [see (12)].

With the basal metabolism data the same conventions are observed as in the presentation of the data of Table VI ("Vital Capacity"). The last three horizontal columns give the percentage distribution of the group into those above, below, and within the conventional normal limits. The presentation of the data of the other measurements does not require explanation.

Beginning with the hypofunctional group, only the gonad and adrenal cases show values above predicted levels, and in no case does the upper deviation exceed normal limits. In the case of the gonad failures, as noted earlier in the text, marked

TABLE XII
RESPIRATORY METABOLISM DATA

Observation	Endocrine														Not End.
	In Glandular Depression						In Glandular Dysfunction					In Glandular Hyperactivity			
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Sum.†	Pit.	Thy.	Pl. Gl.	Uncl.	Sum.†	Pit.	Thy.	Sum.†	
Basal Metabolism—															
High	−4	−10	+9	+4	−29	+9	+33	+18	+7	+18	+33	+23	+87	+87	+27*
Low	−24	−50	−25	−39	−30	−50	−28	−25	−34	−24	−34	+15	+19	+15	−22
% above prediction	0	0	8	15	0	5	11	24	21	15	18	100	100	100	48
Average	—	—	+5	+4	—	—	+8	+10	+6	+9	+8	+19	+45	+32	+7
% below prediction	100	100	92	85	100	95	89	76	79	85	82	0	0	0	52
Average	−15	−23	−13	−14	−30	−19	−12	−14	−12	−12	−13	—	—	—	−6
% above +10%	0	0	0	0	0	0	2	7	0	5	4	100	100	100	7
% between +10% and −10%	23	0	35	62	0	24	42	45	57	37	45	0	0	0	81
% = or below −10%	77	100	65	38	100	76	56	48	43	58	51	0	0	0	12
Temperature—Average	98.0	97.9	98.1	98.1	97.0	97.8	98.0	98.1	98.2	97.9	98.1	98.2	98.2	98.2	98.1
Blood Pressure, Systolic—															
Average mm	118	112	112	95	111	112	111	122	133	115	120	161	138	150	125
% = or over 150 mm	0	1	3	0	0	1	4	6	36	3	12	60	31	46	12
% = or under 110 mm	21	53	60	100	75	62	39	23	21	54	34	0	13	7	19
Diastolic—Average mm	73	72	69	53	68	67	73	74	81	69	74	92	73	83	75
% = or over 100 mm	2	1	1	0	0	1	3	6	21	0	8	40	13	27	7
% = or under 65 mm	23	28	36	100	25	42	20	20	21	35	24	20	44	32	22
Pulse—															
Average	71	69	74	75	69	72	72	77	76	74	75	81	101	91	76
% = or over 80	23	13	34	46	33	30	21	40	43	26	33	60	76	68	36
% = or unde, 70	60	58	37	38	67	52	41	23	43	43	38	20	0	10	34
Respiration—															
Average	14	15	16	15	18	16	15	16	16	16	16	13	18	16	15
% = or over 20	3	7	10	8	67	19	14	14	29	20	19	0	41	21	16
% = or under 10	10	4	8	8	0	6	8	0	14	7	5	0	12	6	12
Alveolar CO—															
Average mm	39	37	34	36	32	36	38	36	36	34	36	38	36	37	37
% over 35 mm	46	62	54	42	33	47	55	49	36	38	45	75	67	71	48
% = or under 30 mm	7	9	35	8	33	18	4	12	29	28	18	0	20	10	13

*Lymphatic Leukaemia. †Summaries are not weighted for number of cases composing each group.

nervous instability is a common feature. As we frequently have had occasion to observe, emotion, even when controlled, may cause an increase in the observed oxygen consumption which can readily assume vitiating proportions.

In the adrenal cases there is a response to fatigue which operates in the same way. As pointed out above, basal rates as observed are maxima with the true value in certain cases lying well below that recorded. Another possible explanation for the exceptions in both series may lie in our inability to define a dysfunctional state. With due cognizance of the downward trend of the energy exchange, the relative magnitudes become suggestive. Recognizing the reenforcing influence that malnutrition may exert in this group (the adrenal cases particularly), it is still apparent that the thyroid exercises the dominant influence, the pituitary and gonad the least, while the adrenal occupies a position between these extremes. The further analysis shows the adrenal to be the only member of the group in which a majority of the cases fall within the conventional limits of normality. Each of these glands will be discussed independently in later papers.

Continuing with the basal rate observations, the dysfunctional group next claims attention. Only the pituitary and thyroid of the single entities are here represented and, as could be predicted, values are found both above and below the calculated norms. The thyroid shows a series of levels produced by the intermediate transitional phases. The pituitary group includes not only such conditions but also those in which the dysfunction is caused by a difference in functional level in the two lobes. This possibility (i. e., of severe malfunction of one lobe) determines the somewhat greater scatter of the pituitary data than those of the thyroid. In the pluriglandular group one composing element is definitely hypo- (ablation) and the other dys-functional, the summation giving predominance to the downward trend. As has already been noted, in many endocrine conditions there is a distinct tendency for an initial over-active state to undergo a functional involution toward a final condition of hypoactivity. This is shown in the separation of the data given above into the three zones of over-, normal, and under-activity.

The hyperfunctional group contains but pituitary and thyroid cases. The results are clear-cut and require but little discussion. The greater influence of thyroid disease on the energy requirement is unmistakably evident. The extremes in the non-endocrine group compare favorably with the values of the dysfunctional moiety. The highest levels are recorded in cases of lymphatic leukaemia, the lowest in malnutrition. Sharp differentiation from the endocrine group comes in the zonal distribution, with 81 per cent falling inside the limits of normality. The relative rarity in this series of those non-endocrine conditions (malnutrition, nephritis with severe edema, febrile states, and leukaemias), which significantly influence the respiratory exchange determines this division.

The temperature values in the several divisions are peculiarly influenced by the undesirable feature of this method of presentation. Slight differences, therefore, are significant. In the hypo-function group, the gonad and adrenal agree with the non-endocrine average, while a downward tendency is shown by the thyroid, which is less marked in the pituitary. The pluriglandular group exhibits the addition effect of the two endocrine agencies involved. In the dysfunctional group the thyroid and pluriglandular units show an upward tendency which, in the case of the thyroid, is emphasized by the state of hyperfunction.

As to blood pressure changes, hypofunction of the pituitary causes mild, of the adrenal severe, hypotension, the thyroid and gonad groups occupy an intermediate position. It is interesting that the late cases of hypothyroidism with arteriosclerosis fail to influence significantly the general average. The dysfunctional group shows upward tendencies, with the exception of the pituitary. The dual character of the gland, with its dysfunction including possibly severe aberration in but one lobe, probably explains the seeming contradiction. The wider limits of variation shown by the basal rate support this view. In the hyperfunctional group the upward progress of the thyroid continues moderately, while the few pituitary cases assume a real hypertensive level. It is doubtful if a larger series would exhibit so marked a degree of increased blood pressure. In the present instance, one severe case could influence the average perceptibly. Actually, three of the five cases presented *hyper-* and the other two *hypo*-tension.

The pulse rates repeat the temperature relationships, with the thyroid showing the major degrees of variation. The respiration rates show a very general uniformity, only the thyroid manifesting any real increase with increasing functional activity.

Throughout the discussion on respiratory metabolism no attention has been paid to the non-endocrine group. A general normal tendency exists and the magnitudes observed are not remarkable.

Alveolar carbon dioxide is regarded primarily as an index of the combining power of the plasma. Two methods for its determination are in general clinical use, *i. e.*, that of Marriott (38), which approximates venous, and that of Fredericia (39), which more nearly expresses arterial tensions. For reasons given elsewhere (40), we prefer the latter method, and the values here recorded are all derived by it. Venous tensions would show values a few millimeters higher. The test is at best a rough one and is peculiarly susceptible to error through incooperation. Failure to expel a representative sample will inevitably lead to low values because of dilution of the alveolar air with dead or even tidal air. While all of the averages are low, only the gonad failures and the pluriglandular group in which castrates predominate show really depressed levels. The same condition obtains in pregnancy, as has been shown by the writer (40) and others, and is of potential diagnostic significance in a study like the present. Low values arising in the presence of ketosis are shown by urine examination, and a retention acidosis caused by severe nephritis is implied where the major condition has been shown to exist.

The sole remaining test of this initial group which remains to be considered is that of the sugar tolerance. For reasons discussed in detail elsewhere (41) we have selected galactose as the material for the test meal. The technique of the test has already been described. Briefly, graded doses of the sugar are administered under standard conditions, and the assimilation limit defined by the quantity necessary to produce a transitory melituria. This is, in essence, the original Hofmeister (42) technique. Blood sugar curves have been discarded (20) as relatively meaningless and lacking the essential quantitative character. The preliminary studies (43) defined 30 grams as the tolerance dose for the normal male under all conditions, while the normal female assimilation limit varies from 20 to 40 grams, depending upon her state of sexual maturity The reasons for this intrinsic sex difference need not be discussed here; the fact is of very marked differential diagnostic value. Briefly outlined, in prepubertal years the female gives slight melituria with 20 grams; with the onset of menstruation the assimilation limit increases and usually in the course of a year reaches 40, the normal adult tolerance. This continues to the menopause, when there seems to be a tendency to regress to an intermediate level of 30 grams.*

During adult years pregnancy will cause a fall in the tolerance, first to 30 and later to 20 grams. A further fall, post-partum, is transitory, and ultimately the normal level is resumed. Menstruation itself shows a tendency to lower the tolerance slightly during the period. Removal of the ovaries restores the prepubertal level of 20 grams.

Since the normal standard for the female is variable and dependent upon the level of ovarian activity, the collective presentation of results from patients representing all of the several developmental stadia must be in relative and not absolute terms. For example, a 40-gram level represents an increase of 100 per cent above the normal for the prepubertal child and is the exact normal level for the healthy woman of thirty years in a state of sexual rest. By reporting the deviation of the individuals from their personal norm in terms of per cent, data are secured which are comparable to each other. In presenting the results of this test (*i. e.,* percentage deviation from the norm), this convention has been adopted. While the male standard remains unchanged through life, the same convention has been followed for the sake of uniformity. In discussing the results obtained, it may not be out of place to repeat that as they are derived from individuals showing wide degrees of variation in functional level, the average values are much less than the deviation shown by individual cases in the series. Mild and severe conditions, with the several intermediate gradations, manifest themselves quantitatively through the amount of their variations from the standard. The method of averages lessens the apparent magnitudes, leaving the expressed tendencies significant in sense and degree. In tests of this character the dysfunctional group, which is made up of mutually compensating units, tends toward a misleading normality. In the effort to minimize these hampering conditions as far as possible presentation is made with the same detail as that employed in the preceding table. The galactose tolerance data are given in Table XIII.

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* The differences are undoubtedly gradual and progressive. In applying the test, it has been found to be practical to vary the several test doses by 10-gram amounts, and this convention defines the figures as given.

NOTES

A. A few cases have been omitted from the tabulation as a concomitant non-endocrine disease influencing sugar tolerance makes them mask the true picture.
   1. One hypothyroid patient (male) at 60 gms. had an advanced chronic intestitial nephritis, and one at 20 gms a demonstrated liver involvement.
   2. Four hypothyroid patients (female) with demonstrated liver disorder average —68%.
   3. Two male castrates at 40 gms. had late chronic interstitial nephritis.
   4. Four hypogonad patients (female), averaging —80%, had severally cases of central nervous lesions (2), syphilis (1), and liver disorder (1).
   5. Three hypogonad patients (female), showing a normal postmenopause tolerance of 30 gms., all had an established nephritis and were over 60 years old.
   6. One hypoadrenal patient (female), with raised tolerance (+25%), had a long established chronic interstitial nephritis.

B. In the pluriglandular cases, 20 gms. is taken as the demonstrated normal tolerance for the castrated female.

In the hypofunctional group failure of the pituitary uniformly produces an increase in tolerance of very marked proportions. With failure of the thyroid the same direction is observed, but both the amount of the increase and the frequency of its appearance fall far short of the pituitary influence. With the testicular failure no change is observed, while with the hypoovarian patients there is uniformly a depression of the tolerance which in the average falls just short of 50 per cent. It is to be remembered that the group herein reported, however, contains only females in whom the menstrual function had been established; in the other words, with sugar tolerances above the prepubertal level. Hypoadrenalism, like gonad failure, seemingly causes a downward tendency and one of even more definite proportions than in the ovarian cases. This observation is at variance with all other reports recorded in the literature and has already been noted in connection with the exhibition of glycosuria

TABLE XIII

GALACTOSE TOLERANCE

Observation	Endocrine										Not End.
	Hypo-functional					Dys-functional				Hyper-functional	
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Pit.	Thy.	Pl. Gl.	Uncl.	Pit.	
Male— High (gms.)	70	40	30	30	—	50	30	—	30	20	40
Low (gms.)	40	30	30	20	—	5	20	—	10	5	10
% above normal	100	14	0	0	—	4	0	—	0	0	5
% dose variation above normal (Av.)	+73	+33	—	—	—	+50	—	—	—	—	+33
% =normal	0	86	100	67	—	12	33	—	33	0	41
% below normal	0	0	0	33	—	84	67	—	67	100	54
% dose variation below normal (Av.)	—	—	—	−33	—	−50	−33	—	−50	−53	−40
Female— High (gms.)	120	60	30	40	50	80	40	60	40	20	40
Low (gms.)	40	30	20	5	20	5	20	5	20	20	5
% above normal	100	38	0	0	50	7	0	15	0	0	0
% dose variation above normal (Av.)	+72	+29	—	—	+100	+85	—	+75	—	—	—
% =normal	0	62	0	17	25	1	70	15	11	0	42
% below normal	0	0	100	83	25	92	30	70	89	100	58
%dose variation below normal (Av.)	—	—	−45	−52	−25	−52	−25	− 6	−35	−50	−39
Summary											
% above normal	100	32	0	0	50	6	0	15	0	0	2
% =normal	0	68	*100	33	25	5	56	15	17	0	41
% below normal	0	0	†100	67	25	89	44	70	83	100	57

* Male. † Female.

in some of these cases. The fact only is recorded here and will be discussed more appropriately in a later paper. The pluriglandular cases exhibit the result of summation of the several diverse agents comprehended in the group.

The data in the dysfunctional group include only the pituitary, thyroid, and the pluriglandular cases. The transition influence is manifested with the pituitary, a few of the cases having been examined at a time when they were passing through the zone of normality. A persistence of an earlier overactivity is shown by the thyroid group with 44 per cent of the cases exhibiting a lowered tolerance. In the pluriglandular group the ovarian element is more in evidence than in the hypofunctional fraction in which pituitary failure dominated the series.

It is to be regretted that hyperthyroid cases do not appear in this summary. As was stated earlier, this condition does not ordinarily require so elaborate an investigation for the establishment of a diagnosis. The sugar test requires three days, and when a diagnosis could be made by a morning's study, co-operation was not obtainable for this time-consuming addition. Since this series was completed a few hyperthyroid cases have been given the sugar test. They confirm, in the main, the inference to be drawn from the two groups here presented, namely, a moderate lowering of the tolerance. Lowered tolerance with cases showing overactivity is seemingly of more frequent occurrence than is the converse in thyroid failure. A warrantable inference from this fact would be of the possible production by the thyroid of a second hormone acting on carbohydrate metabolism as thyroxin—or something related to it—may be regarded as regulating the energy metabolism. The hyperpituitary cases exhibit a strait antithesis of those showing failure. The practical abolition of any tolerance for galactose is the common finding in severe cases of overfunction.

A word in passing may be offered on the frequent association in the literature of pituitary disease with diabetes. That it is in some measure an outgrowth of the untrammeled speculations of the Viennese school admits no doubt, but it is perpetrated by several writers who patently do not subscribe to the theory of an interlocking glandular directorate. If the lowered tolerance of the acromegalic is but an expression of direct inhibition of the function of the islands of Langerhans, then consistently, in hypofunction of the former the increased sugar tolerance must signify an augmented production of insulin or lessened inhibition of its activity. In one of our cases, not reported in this series, the galactose tolerance was 300 per cent above the normal. This should imply at least an equal increase in available insulin, the sequel of which would but ill accord with the typical pituitary obesity and the normal blood sugars. Many other arguments are adducible, but they may be left more fittingly, to later discussion. That influence on carbohydrate metabolism is not confined to the endocrine group is apparent from the table. Lowered tolerances predominate—the few high values being seen in advanced nephritis. In the group characterized by a lessened power of assimilation are found cases presenting various lesions of the central nervous system, syphilis, primary anaemia, liver disorders, malignant neoplasm, and psychoneuroses. The wisdom of excluding such fairly frequent disease conditions before interpreting a sugar test in terms of endocrine disorder should not require comment.

Before leaving this portion of the work, certain correlations may prove of value. In presenting them not only will the summaries already presented be considered, but, equally, individual cases representing extreme conditions. These latter must take first place, as in them one finds the extreme limits defined, and hence the functional tendencies illustrated most clearly. Equally, it must be borne in mind that in selecting the extreme case many features may present that in early and intermediate states do not occur in really significant magnitude. Such presentation, therefore, must be used with due caution when applied to the individual case.

TABLE XIV

PHYSICAL MEASUREMENTS

Influence of Hypofunction

	Pituitary	Thyroid	Gonad	Adrenal
Height	— — —	— — —	(+ +)	?
Sitting Height Index	— —	+ +	— —	?
Weight	+ + +	+ +	+ +	—
Lung Volume.......	—	— — —	—	—

To allow compact form, the data will be reduced to tables. In the interest of simplicity only hypofunctional tendencies will be listed, as the known and established hyperfunctional conditions present in the main antitheses to the former. Dysfunctional states present too many permutations of the extreme types to be easily presentable. Records from the literature, not observed in this series, are enclosed in brackets.

Pituitary and thyroid dwarfism are coupled with the overgrowth of the long bones said to occur from castration in childhood (males only). A clear-cut adrenal influence has not been defined. The values for the sitting height index are probable but not certain. The weight relation seems fairly well established and that of the lung volume definitely so.

The urine values are insusceptible to this form of analysis. The urines in pituitary and gonad cases tend toward the normal, those with thyroid disease simulate, and those with adrenal malfunction define the picture of nephritis. This adrenal tendency is well marked in the urea curve. In the nitrogen partition the thyroid and adrenal cases show the greatest tendency toward high residual fractions and absolutely high values as well. The pituitary influence is indeterminate, the gonad picture tends toward normal.

The high blood uric acid of the pituitary cases, and high residual nitrogen and low blood sugar of adrenal disease, are the outstanding features of this group of analyses.

The general low white count and lymphocytosis, the latter most marked in adrenal, though frequently assuming high values in thyroid cases, and the eosinophilia of the pituitary and adrenal cases, are the most salient features of the blood morphology.

The accessory physical measurements incident to the respiratory metabolism may be presented in tabular form.

TABLE XV

PHYSICAL FUNCTION

Influence of Hypofunction

Datum	Pituitary	Thyroid	Gonad*	Adrenal
Temperature	—	— —	0	0
Pulse	—	— — —	0 or +	0
Respiration	0	— —	0 or +	0
Blood Pressure.......	—	— —	— —	— — —
Alveolar CO_2.........	0	0 or —	— — —	0 or —

* Ovary only. The loss of the testicles in adult years lowers blood pressure and pulse rate slightly, but seemingly does not produce any marked effect in man.

The average pituitary case shows a generally normal trend, the thyroid a depression varying only in amount, ovarian failure produces a marked drop in blood pressure and a unique depression of alveolar carbon dioxide, while hypofunction of the adrenal exhibits a significant departure from normal only in its extremely low blood pressures.

As a point of differential significance the joint consideration of basal rate and sugar tolerance shows both qualitative and quantitative relations which are highly informative.

TABLE XVI

COMPARISON OF OXYGEN AND CARBOHYDRATE METABOLISM

Influence of Hypofunction

Datum	Pituitary	Thyroid	Gonad	Adrenal
Basal Rate.........	—	— — —	—	— —
Galactose Tolerance.	+ + +	+	— —	— — —

Of the gonads only the ovary again is considered. Ablation of the testicles in adult years produces but a slight drop in the basal rate and no change in sugar tolerance. The differential features of the above scarcely require comment. One condition is frequently met that cannot be resolved by the above relationship. Many women are seen who show a basal rate of from —15 per cent to —20 per cent, and a sugar tolerance of 20 grams. These data could be due either to primary hypogonadism or to the common type of pituitary dysfunction with the anterior lobe under-, and the posterior, over-active. The remainder of the laboratory and clinical picture is absolutely essential to resolve the problem, the initial outcome many times being to establish no more than a greater probability for one or the other diagnosis.

With the foregoing expository statement concerning those tests whose character permits in some measure this form of presentation, attention may next be given to the group of special examinations.

In the main, these are chiefly serviceable as indicating the presence or absence of a non-endocrine disease state to which both the patient's presenting symptoms, as well as the results of certain of the laboratory tests, might be attributable. Exceptionally, such examinations may give positive evidences of endocrine significance, and to these the following discussion will be limited. Before taking up details, however, a brief review of the extent of the special examinations may be presented in tabular form.

TABLE XVII

SPECIAL EXAMINATIONS

Examination	Cases Examined	Positive Findings No.	Positive Findings %
Eye	596	460	87
Ear	206	60	29
Barany	100	25	25
Audiogram	121	111	92
Nose and Throat	40	23	58
Heart (1)	26	14	54
Pelvic	161	54	34
Cystoscopic	14	7	50
Orthopedic	13	12	92
Neurological	310	169	55
Skin	20	20	100
Endermal	47	25	53
Biopsy	6	4	67
Sputum	15	3	20
Duodenal Function	8	3	38
X-Ray (General) (2)	633	362	58
X-Ray (G. I. Series) (3)	30	14	47
Miscellaneous	240	..	..
Total	2586		

(1) An electrocardiograph was not available at the time this series was completed.

(2) Each of these cases had a series of x-ray plates. Pictures of sella, sinuses, and thyroid were always secured and frequently chest, measured heart, and other plates were added.

(3) The Graham test had not been described at the time this series was completed.

It will be seen from the above tabulation that the average of special examinations for each case falls between 2 and 3. Since this series was completed additions to the staff, together with increase in equipment and inclusion of new methods, has augmented this phase of the work. At the present time the long form cases average 8+ and the short form studies 5+ consultations.

The special examinations yielding positive information as to endocrine status may be taken up seriatim.

1. *Liver Function:* These studies—and more significantly the later investigations which have profited greatly through the application of new methods, the products of this and other research institutions—have demonstrated a frequent incidence of liver dysfunction in thyroid failure. There is not necessarily an earlier history of icterus nor of symptoms pointing to liver or gall bladder disease. The Graham test (44), icteric index (45), van den Bergh reactions (46), and more especially the elaborate methods based upon the examination of the duodenal contents which have been devised by McClure (47), give many channels of approach for the resolution of this problem. Such a liver condition may mask the otherwise clear-cut evidences of thyroid disease (modified sugar tolerance, atypical blood picture), and render a diagnosis uncertain. The condition is usually functional in character and frequently yields to duodenal lavage. Migraine of hepatic origin is frequently a concomitant picture.

2. *Ophthalmological Examination:* The production of ocular disturbance by pituitary tumors has been frequently recorded [Josefson (48), Cushing and Walker (49), de Schweinitz (50)], and even through temporary enlargements, as in pregnancy [Erdheim and Stumme (51), Carvill (52)]. Others have recorded changes even when no tumor growth could be demonstrated, and Oppenheim (53) has suggested the existence of a circulating toxic substance derived from the gland and producing optic nerve degeneration. As reported by Rowland (54), a yellow color of the discs, enlarged blind spots, and contraction of the form and color fields are frequently observed in pituitary disease in the absence of demonstrable tumor growth. One or more of these phenomena may also be found in thyroid and gonad involvements, though with less frequency than in the pituitary cases. That the general metabolic disturbance is a direct causal element is seemingly capable of demonstration. The pituitary, from its anatomical relationships, exercises influence through two channels, the others presumably through but one. Other

manifestations, such as cutting of the upper form fields and marked concentric contraction of the form and color fields have been recorded and are shortly to be discussed in the literature. Besides the direct endocrine indications, many evidences of non-endocrine disorders may be elicited in thorough eye examinations. In skilled hands the eye examination is probably more generally suggestive and informative than any other one special examination both in endocrine disease and in other non-endocrine localized or general derangements.

3. *Electrocardiogram:* It has been shown by Thacher and White (55) that thyroid failure may produce a more or less characteristic electrocardiographic picture; these findings have in part been substantiated in our clinic.* An interesting feature is the restoration of the picture to the normal under thyroid medication (see later paper on the thyroid).

4. *X-Ray:* Aside from the large amount of information concerning non-endocrine conditions which this form of examination offers, there are potentially certain direct evidences which should be expected. Lack of epiphyseal union or premature closure are instructive and may support other evidences of aberrant growth relations of endocrine origin. Substernal thyroids may be shown by this means, and the information is of supplementary value.

Sella pictures are of value only when actual erosion of the clinoids or floor has taken place as the result of pronounced hyperplasia. In the great majority of pituitary cases, however, a normal sella is seen—if such a term be warranted to describe a bony structure so variable in its formation [see Camp (56)].

Equally, the diversity of outline of sellae enclosing wholly normal glands suggests caution in the establishment of a pituitary diagnosis on the evidence of a possible abnormal configuration of this structure alone. Thymus shadows, while possibly informative, lack specific indication. Aside from the lack of evidence of a true endocrine function of this gland, certainly in adult years, so-called persistent thymi are found to be far more frequent in necropsy reports than certain clinical writings would seem to indicate. They have been frequently observed in individuals of adult and advanced years who have shown no other evidence of a status thymico-lymphaticus.* It would seem equally plausible to regard a persistent thymus, in some cases at least, as but one evidence of a growth anomaly incident to an established endocrinopathy known to influence development. Further, it may be regarded as a resultant element in status lymphaticus rather than the causal factor.

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* Reid. Unpublished data. Personal communication.

One other finding under this caption requires brief comment. The inclusion of the pineal in the endocrine group is still open to question. Dandy's experiments (57) fail to show any real endocrine influence. Parenthetically it may be said that complete extirpation experiments that yield negative results are by far the most decisive; positive evidences may be produced by trauma to adjacent parts or to other agencies unassociated with the primary object of the experiment. In this series, 29 cases were reported with x-ray shadows interpreted as calcified pineal glands. The etiological classifications gave:

Not Endocrine	9
Pituitary Dysfunction	14
Pituitary Hypofunction	3
Gonad	2
Unclassified	1

In none of these cases was there demonstrable any stigmata which could be associated with the conventional evidences of pineal disease, nor did any of the histories contain suggestive records. It may be argued that all of the subjects were adults and that the pineal condition had probably occurred only after maturation. Such a position is tenable but equally if adopted leads to the inevitable corollary that in adult years, at least, the pineal has no striking endocrine function. While pituitary cases constitute over one-half of the group, it must remembered that there were 270 of them who showed no pineal shadows—and that, further, many of the other patients did not have x-rays of the skull.

5. Such endocrine data as may be elicited by neurological, pelvic, and skin examinations are too well known to require elaboration in this report.

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* Personal communication from Dr. George Burgess Magrath.

The many other observations listed are primarily important, as was stated above, in defining concrete disease conditions unassociated with the endocrine glands.

A few additional words may be permitted before bringing this first paper to its conclusion. The author wishes to emphasize that this can be at most but a preliminary communication. He may say with perfect candor that he is as acutely aware of the many shortcomings of this work as can be any of his readers. That it is the first formal presentation of investigations begun in 1912 is an earnest of good faith. What it embodies may be briefly stated. Certain objective criteria have been established for the determination of the presence of endocrine disease, and, further, its allocation to the individual gland at fault. Equally, it has been shown that a variety of non-endocrine conditions may simulate endocrine diseases both in some of their many clinical aspects, and equally in certain of the significant laboratory findings. In other words, for the establishment of the true etiology it is essential to conduct a general diagnostic study with the possible endocrine element determined only by exclusion. We have applied the method to the study of nearly 3,000 cases with results that seem to us encouraging, even while we recognize the limited amount of real knowledge yet available and the vast extent of the territories still unexplored. It is our hope that application of the correlations here presented may prove of some service to our colleagues in the resolution of their own problems. This independent application is essential to establish such worth as may lie in this method of approach.

Effort has been made to avoid controversy. Where the findings are at variance with conventional endocrine doctrine, the observed and tested facts upon which the conclusions rest are offered to speak for themselves. Many points of first importance must still be largely matters of interpretation, but at least objective data offer a firm foundation for a common starting point.

In conclusion, the writer wishes to pay his heartfelt tribute of thanks and appreciation to the many who have participated in this work. In the first place, thanks are due to those volunteers in the early days whose willing co-operation made the establishment of the normal standards possible; an even greater measure of appreciation is offered to those who in suffering and with disease heavy upon them gave a gracious and willing aid that others might profit where they could not. Every tribute must be paid to the laboratory staff of the Evans Memorial, by whose skilled and patient hands the tens of thousands of exacting and delicate operations have been performed with consistent accuracy. And finally, a basic indebtedness is acknowledged to the group of friends, colleagues, and fellow workers, the full staff of the institution, whose generous assistance, highly skilled service and unfailing support and encouragement have made this work possible.

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Note.—In presenting the foregoing material no attempt has been made to embody a review of the existing literature. Individual citations pertinent to the thesis in hand have been included, but the huge volume of published work in this field makes even cursory notice far exceed the limits of publication. Excellent bibliographies are to be found in a number of works that have appeared in recent years, and to these reference is made for those who desire a more extended review of recent publications. Citations from the author's own work would be over numerous but for the fact that they are expository to the thesis in hand. The present paper is confined to describing a method and reporting certain results obtained with it. Conflicting views will be discussed at greater length in the later papers to which such material more properly belongs.

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STUDIES OF THE ENDOCRINE GLANDS*

II. The Pituitary

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Part I

In a recent communication one of us (Rowe, 1) has presented the details of an objective method for the differential diagnosis of endocrine disorders, together with an analysis of a series of one thousand cases to which it has been applied. The present paper deals with the results obtained in the study, by this method, of a series of cases, four hundred in number, in which some form of pituitary malfunction was demonstrated as a primary etiological factor. As the full details of the method have been published in the earlier communication, it is enough here to state that a very thorough physical examination and the compilation of a detailed medical history are supplemented by a long series of laboratory tests, the significance of which has been demonstrated by elaborate preliminary studies. In addition, detailed examinations by the specialists of the consulting staff give supplementary information concerning indications of endocrine disease, and, even more significantly, the presence or absence of disorders of a non-endocrine etiology. The inadequacy of a single observation to establish a diagnosis except in the rarest instances has already been stressed in the preceding paper. Individual objective facts gain diagnostic significance only as they are interpreted in the light of a large number of correlated observations and measurements. Facts elicited are interpreted in terms of endocrine malfunction only after every known non-endocrine cause has been eliminated by observation and test. This does not preclude the recognition of coexisting endocrine and non-endocrine disorders, but does prevent grave omissions on the one hand, and seriously misleading diagnoses on the other. In a shortly forthcoming paper on non-endocrine disorders, cases illustrative of this point will be presented. In one, the entire picture, save only the blood morphology, was typical of thyroid dysfunction. The case was one of leukaemia.

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*Presented at the Annual Meeting of the Association for the Study of Internal Secretions, Atlantic City, N. J., May 26, 1925.

In presenting this material no attempt can be made at a survey of the literature. The compendious monographs of Cushing (2), Blair Bell (3), Engelbach and Tierney (4), Falta (5), Biedl (6) and others, together with the series of excellent articles in ''Endocrinology and Metabolism'' (7), give reviews which are as complete as the rapidly growing literature will permit. When to these earlier compilations are added the several hundred titles that yearly appear, the impossibility of adequate presentation is obvious. Reference will be made only to contributions, the details of which bear directly on the thesis in hand. Omission of recent papers implies no adverse opinion of their merit.

The present series of four hundred pituitary cases is selected from nearly two thousand patients referred for diagnosis. The presentation of so large a mass of data within reasonable compass offers manifest difficulties. The tabulation of averages offers the simplest solution, but here, in some measure, the means defeats the end. The algebraic summation of the results of opposing influences by its very nature destroys the magnitude and direction of deviations from the conventional normal which are of diagnostic significance. To illustrate: a judiciously blended group of extreme thyrotoxicoses and myxedemas would exhibit a strictly normal average basal rate. Further, in any group of cases but a few will be of an advanced order, and the inclusion of many incipient cases betraying tendencies rather than an established condition will lessen the average magnitudes and hence the apparent significance of variation. On the other hand, with an adequate number of cases, because of these limiting conditions, variations of relatively small amount may assume a real significance.

An added complication arises, in the present instance, from the fact that the hypophysis consists of at least two, and possibly four, functional entities.

Waiving, in the interest of simplicity, the subtleties of dialectic, we shall designate as ''hyperfunctional'' those cases in which the observed facts equate with what is generally conceded to be the evidence of an over-activity. Equally, the ''hypofunctional'' group show a picture of relationships the opposite of the foregoing. The cases designated as ''dysfunctional'' are those in which the two lobes are demonstrably not at the same functional level, and includes those cases in which one or both lobes are undergoing functional involution.* This group contains a wide variety of conditions determined by the relative functional variations in two bodies, each with three potential levels of activity and seemingly well differentiated as to independent influence on metabolism. As might well be predicted, a very large percentage of the cases here reported fall in this category.

Yet another element of confusion arises from the fact that different disease pictures are engendered by the relation of the time of development of the glandular malfunction to the age, and particularly to the sex status of the individual. These differences have been well recognized and so frequently described as to require no further elaboration here. That the intermediate or end results of a given pituitary aberration will be greatly influenced in certain directions by the maturity of the individual, is established, and in any scheme for the presentation of data, sufficient differentiation must be employed to take cognizance of significant variations.

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*The shifting sugar tolerance during the progress of acromegaly, so clearly demonstrated first by Cushing and his associates (8), is a case in point.

Recognizing the limitations implicit in this method of presentation of data, it remains only so to order the arrangement as to reduce these obscuring conditions to a minimum. While the group contains few of the spectacular cases of extreme malfunction which have been reported from other sources, all of the earlier cases, the study of which laid the foundation of the present generalization, exhibited clear-cut and unmistakable lesions demonstrated by previous surgical intervention, radiography or subsequent necropsy. Well established acromegaly prior to the onset of the involutional changes, is usually unmistakable. But the same definition is lacking in the other syndromes which bear the names of Froehlich, Lorain-Levi, and others.

From the clinical standpoint there is a certain possibility of confusion in the hypofunctional states of several of the endocrine group, and only by objective methods of great completeness of detail can they be differentiated with any measure of certainty.

Turning to the results of the study, the various physical measurements have been collected in the following table. The highest and lowest values observed for each measurement are included as giving an idea of the range of variation in each of the several quantities. In conformity with the convention discussed above, hypofunctional states are designated as "—," the complementary hyperactivities as "+," while the several types of dysfunction are grouped under the caption "±." The summary values are, in many instances, unduly influenced by the relative numerical preponderance of the dysfunctional group. The use of unweighted averages, however, would only introduce a different disturbing element.

In discussing these data it must constantly be borne in mind that the magnitudes recorded are possibly influenced by wholly extraneous factors of which no cognizance may be taken. Such an element as the percentage distribution of different races presenting widely different characteristics,* could well modify data obtained by two independent investigators. The seeming predominance of females over males in this series may be due to an inherent greater susceptibility on the part of the female, and equally could be referable to a greater frequency of recourse by that sex to medical aid. Our figures showing a greater incidence of the "hyper"-functional state in the male are not in accord with the far more comprehensive observations either of Sternberg (9) nor of Hinsdale (10). Our larger series of hypo- and dys-functional cases accord with the frequently recorded observation of a greater incidence in the female. Whatever the cause, the fact remains that in this group the females predominate in ratio of 3 to 2. The small number of the true hyperpituitary group makes certain of the absolute magnitudes of somewhat less significance than with the other two divisions. The differences in relative physical proportions of the two sexes comes in as an obscuring factor in the absolute figures here recorded. Both the relation of Sitting to Total

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*In this connection, to ascribe racial peculiarities to varying levels of endocrine function, wholly ignoring the manifest influences of environment, nutrition, and climate, shows more enthusiasm than judgment. Further, these ethnic groups fail to show many of the bodily peculiarities that their alleged endocrine origin would presuppose.

TABLE I

PHYSICAL MEASUREMENTS

Observation		Unit	Gland Function			Grand Average
			−	±	+	
Number of Cases		400	**83**	**310**	**7**	
Sex	Male	%	**29**	**36**	**57**	**40**
	Female	%	**71**	**64**	**43**	**60**
Age	High	years	71	70	63	
	Low	years	9	6	17	
	Average	years	**32**	**33**	**42**	**33**
Height	High	cm.	195	189	172	
	Low	cm.	130	103	155	
	Average	cm.	**165**	**164**	**166**	**164**
Sitting Height	High	cm.	100	99	91.5	
	Low	cm.	69	56	85	
	Average	cm.	**87**	**87**	**88**	**87**
Sitting Height Index			**0.527**	**0.530**	**0.530**	**0.530**
Chest Girth	High	cm.	128	145	98	
	Low	cm.	58	54.5	67	
	Average	cm.	**86**	**81**	**84**	**82**
Weight	High	kgm.	150.0	180.0	78.8	
	Low	kgm.	21.6	15.7	54.9	
	Average	kgm.	**73.7**	**66.3**	**65.6**	**67.8**
Area	Average	sq.m.	**1.81**	**1.72**	**1.73**	**1.74**
Lung Volume	High	c.c.	6200	5400	3600	
	Low	c.c.	1330	600	2380	
	Average	c.c.	**3050**	**2900**	**3050**	**2930**

Height (Sitting Height Index) and of the former to the chest girth (not here reported), are definitely different in the two sexes. Presentation on a sex basis would, however, multiply data without adding much to the significance of the picture.

Clarity of outline can be secured by relative figures, using two sets of standards for the sexes, and this has been done in the later tables wherever it is found to be informative. The only really salient sequence here traceable is in the greater tendency toward obesity with the lower activities, and even here the heaviest subject was a boy weighing 180.0 kgm., with a pituitary dysfunction of the type most common in our experience in which the anterior lobe is under-, the posterior, overactive.

The apparently greater age of the hyperfunctional group accords well with the general observation of the more frequent occurrence of this condition in adult years, and the frequent prepubertal appearance of glandular failure.

As was stated above, absolute values are influenced by several extraneous factors, to allow for which would entail a complexity that would obscure the issue. Certain correlations have been suggested which allow for sex and occupational differences by the establishment of graded standards. One set of such correlations have been suggested by Dreyer (11). As one of us (12) has shown, only the Dreyer comparisons based on Sitting Height (designated ''Trunk'' by the author) are significant, the other correlations leading to exterpolations of a most misleading character. Further, it is a better practice to use but one occupational standard for each sex, varying the limits of tolerance to accord with individual habit. We have adopted Dreyer's male ''A'' and female ''B'' standards as most nearly conforming to observed American conditions. West (13) has also established correlations between lung volume (designated ''Vital Capacity'' by Dreyer), area, and standing height. Our practice has been to report the average of the Dreyer value with the average of the two West comparisons. By so doing a weight factor (through the area) is introduced without leading to the absurd values of Dreyer's weight comparison. For the reason given above, only West's male and female standards are used. With both the West and Dreyer comparisons it has been found that the female standards accord better with male children than do those of the adults of their own sex. The results of these comparisons are given in Table II.

TABLE II

"VITAL CAPACITY" COMPARISONS

Observation		Unit	Gland Function			Grand Average
			−	±	+	
Weight	High	%	+123	+179	+28	
	Low	%	−23	−42	−11	
	+ Average	%	**+33**	**+27**	**+13**	
	%	%	73	62	71	65
	− Average	%	**−9**	**−13**	**−8**	
	%	%	29	38	29	35
	Net Average	%	**+22**	**+12**	**+7**	
Chest	High	%	+52	+65	+16	
	Low	%	−15	−24	−13	
	+ Average	%	**+14**	**+12**	**+7**	
	%	%	76	63	71	66
	− Average	%	**−7**	**−7**	**−7**	
	%	%	24	37	29	34
	Net Average	%	**+9**	**+5**	**+3**	
Lung Volume	High	%	+18	+20	−13	
	Low	%	−56	−62	−31	
	+ Average	%	**+8**	**+6**	—	
	%	%	19	10	0	11
	− Average	%	**−21**	**−22**	**−19**	
	%	%	81	90	100	89
	Net Average	%	**−16**	**−19**	**−19**	

The values given above possess a certain definite significance. The tendency of the pituitary case to over-weight is clearly shown, as well as the influence of the level of functional activity on this manifestation. The correlations between chest and weight are excellent. While the girdle type of obesity that suggests pituitary malfunction should influence the chest less than the hip measurement, increase in girth of the former may confidently be predicted.

The depression of observed over calculated lung volume is definite, and again might well be anticipated. Peabody (14) has shown the depressing influence of cardiac disease and of general weakness, and other writers have made similar observations (15). The significance here is in the relatively slight diminution (slightly less than one-fifth) of the predicted capacity. Further, the value is probably in excess of the truth, as the general obesity in this condition makes the West normal standards somewhat high. No correction is made for this, however, as the results thus obtained are better suited for the demonstration of diagnostic differences in cases as actually met in practice.

The end results of certain phases of metabolism can best be evaluated by analysis of the urine, and certain of the observations permitting of tabular presentation are collected in Table III.

TABLE III

URINE MEASUREMENTS

Observation		Unit	Gland Function			Grand Average
			−	±	+	
Volume	High	c.c.	5800	3680	2000	
	Low	c.c.	330	350	860	
	Average	c.c.	1360	1150	1280	1190
Spec. Grav.	High		1.036	1.039	1.028	
	Low		1.005	1.007	1.012	
	Average		1.018	1.019	1.019	1.019
Albumin		%	19	25	57	24
Casts		%	11	18	43	17
Sugar		%	0	25	71	
'Urobilinogen"		%	21	29	71	29
Amylase Index	Average		19	18	20	18
Salol	Average	min.	72	70	81	71
Urea Curve	Normal	%	54	50	0	49
	Delayed	%	14	11	33	12
	Progressive	%	5	7	0	6
	Low	%	27	32	67	33
Phenol Sulphone Phthalein, 2-hour Elim.	Average	%	52	51	55	51

While the dissociation of diabetes insipidus from pituitary disease, suggested, among others, by Houssay (16), and more recently by Bourquin (17), as deriving from injury to the mammillary bodies, eliminates this condition in some measure from a priori inclusion in the hypophyseal group, it does not preclude the frequent observation of a pituitary polyuria. The contiguity of the controlling bodies to the endocrine gland implies frequent damage to them secondary to hyperplasia of the pituitary.

Elimination here is seen to be fairly normal in spite of an appreciable number of cases of lowered kidney permeability demonstrated by the other observations. The sequential relationship of the appearance of albumin and casts is well illustrated in the percentages of the three groups. Even more strikingly does the incidence of glycosuria as an evidence of posterior lobe over-function manifest itself. This finding has been very frequently recorded, although many of the observers, even the more recent, persist in regarding the condition as a diabetes engendered by pituitary influence on the pancreas. The untenability of this position is soon to be discussed at length elsewhere.*

A striking and significant finding in this group of cases is the positive response of the urine to para-dimethylamino benzaldehyde, the ''urobilinogen'' test of Ehrlich. That this response depends upon the presence of urobilinogen, is hardly probable. Positive tests have been demonstrated by many in a variety of liver conditions, and one of us (1) has shown it in primary anaemia. Like so many color reactions in which an organic complex is the reagent, the test lacks in specificity and may well be given by a series of substances which need have only a single organic group in common. Its appearance in cases of pituitary disease is of a definite diagnostic import when the non-endocrine causes have been experimentally ruled out. The Salol test, of no great significance, approaches normality. Designed as a rough test of gastric motility, it is primarily dependent on kidney permeability. The provocative urea curves agree in substance with the urine analyses in implying a lowered level of kidney activity, and the Phthalein test offers such measure of confirmation as may be derived from any test subject to so many extraneous disturbing influences.

Summarized, it may be said that a disturbed kidney function seems to be concomitant to pituitary malfunction—probably by indirection through general metabolic disturbance,—that posterior lobe over-function frequently produces a glycosuria which is not diabetic, and that a positive response to para-dimethylamino benzaldehyde is shown by nearly one-third of the cases in this series.

It has been the practice of this laboratory to make nitrogen partition examinations on all urines analyzed. This serves the two-fold purpose of estimating the nutritional level of the patient,† and of indicating metabolic disturbance in abnormality of the partition formula. As has been pointed out by one of us (18), it is not necessary to carry out an elaborate nitrogen metabolism experiment for these data to assume significance. The relative amounts of the several constituents in health depend, as was first shown by Folin (19), on the total nitrogen elimination, the endogenous and exogenous moieties of the several factors determining relative losses with lowered protein intake. The data from the nitrogen partitions are given in Table IV.

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*Rowe, "Non-Diabetic Glycosurias." In preparation.

†For example, the obese patient who acknowledges a food intake of a glass or two of milk in the twenty-four hours, and whose 24-hour urine contains 25 grams of nitrogen. Equally valuable is the recognition of a partial protein starvation with its far reaching effects.

TABLE IV

NITROGEN PARTITION

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Total Nitrogen...........Av....	gms.	9.37	9.28	10.98	9.33
Urea Nitrogen............Av....	%	79.9	80.3	77.8	80.2
Uric Acid Nitrogen........Av....	%	2.2	2.1	1.6	2.1
Ammonia Nitrogen........Av....	%	4.3	3.7	4.8	3.8
Creatinin Nitrogen........Av....	%	4.6	4.5	4.4	4.5
Residual Nitrogen........Av....	%	9.0	9.4	11.4	9.4
% of Cases = or > 9%.........	%	39	54	71	51

The nitrogen averages show a general level of protein utilization well above Sherman's (20) maintenance level. It is true that they do not indicate a "luxury" consumption, but it should be borne in mind that the majority were hospital patients.

[For reasons that have never been fully explained, the average person during a hospital residence drops to a lower nutritional level for protein than his usual habit elsewhere. This is not due to any change in the dietary *per se;* it is our routine practice to give the patient not less than 1.5 grams of protein per kgm. body weight.* With the average weight as a basis, this would correspond to an elimination of some fifteen grams of nitrogen—making allowance for the fraction not absorbed. The actual output is but 60 per cent of the predicted. The phenomenon has been observed by every worker in this field, but so far as we know no attempt at an explanation of it has appeared.]

As the result of a long series of observations, partial report of which has already appeared (18), the residual or undetermined nitrogen partition has been assigned a value of 9 per cent as the upper limit of normality. Folin (19) found values less than 8 per cent when the nitrogen output was reduced to less than four grams, but as the quantity is obtained by difference and incorporates all the analytical errors for the determined constituents, the higher value is felt to be more representative.

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*Needless to say, in cases like that of our eleven-year-old boy weighing nearly four hundred pounds, this schedule fell far short of realization.

All of the groups show a level indicative of disturbed metabolism, and this is more marked in the hyper-active group, both in amount and in frequency of occurrence. If the hypoactive condition represented the terminal phase of a cyclic change—as is certainly partially the case in acromegaly—this might well be expected, the body re-establishing a new metabolic equilibrium at a lower level with the subsidence of the abnormal activities. This will not account for all cases but raises an interesting point for speculation in regard to a certain proportion of them. Another interesting feature is the relative and absolute increase in the uric acid elimination in the hypofunctional group. Falta and Nowaczynski (21) have noted an increase in uric acid output in acromegaly, but found a lowered elimination in a single case of head trauma which they diagnosed as "dystrophia adiposo-genitalis" from a tumor in the region of the hypophysis. In this latter instance the question may well be raised if this single patient may be regarded as typical of true pituitary disease. In the study on the residual nitrogen already cited, it has been shown that while the high values are due in part to increase in the amounts of substances normally present in very low concentration, there yet remain significant amounts of nitrogen which cannot be allocated to any known constituent. The nature of this residuum is now under investigation.

As the blood is the forerunner of the urine, the results of the routine examinations of fasting blood may next be considered.

In the main it will be seen that the blood chemistry bears out the implication of the urine findings as to the functional capacity of the kidney. The most striking feature is the high value for uric acid, and more particularly the large percentage of cases showing a high uric acid with normal levels for the other nitrogenous constituents. Some years ago Hammett and his associates (22) observed an increase in blood uric acid in four out of six experimental subjects to whom desiccated pituitary extract was administered per os. The present results leave no doubt that a high blood uric acid, independent of the other nitrogenous elements of the blood and not deriving from nephritis or gout, is found in disease of the pituitary. The diagnostic significance of this fact is important.

TABLE V

Blood Chemistry (and Serology)

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Non-Protein Nitrogen.....Av....	mgm.	**32**	**33**	**36**	**33**
% > 35 mgm................	%	22	25	57	
Urea Nitrogen...........Av....	mgm	**15**	**16**	**17**	**16**
% > 17 mgm................	%	12	16	29	
Uric Acid...............Av....	mgm.	**3.6**	**3.8**	**3.8**	**3.8**
Net* % = or > 4 mgm.......	%	24	33	20	31
Creatinin...............Av....	mgm.	**1.5**	**1.5**	**1.6**	**1.5**
Residual Nitrogen........Av....	mgm.	**15.2**	**15.1**	**17.1**	**15.1**
Sugar...................Av....	mgm.	**97**	**95**	**93**	**95**
% > 120 mgm...............	%	1	1	0	1
% < 80 mgm...............	%	1	5	0	4
+Wassermann.................	%	0	0	0	0
+Kahn (presumptive)..........	number	0	0	0	0
+Spinal Fluid..................	number	0	?	0	?
+Schwartz-McNeil.............	number	0	1	0	1

An interesting result is the normal blood sugar observed and, particularly, that the hyperfunctional group present the lowest average. In a single case which we have had under continuous observation for over four years, and which is to be described in detail elsewhere as well as noticed in this paper, we have recorded high blood sugar levels. These were the result, however, not of the pituitary tumor per se, but possibly to injury to the brain produced during treatment or the coexistence of a true diabetes. The details on this case (S-326, B-269, B-475) will be given briefly later in this paper. It will be noted that one case in the series is reported with a questionably positive spinal fluid examination. There was an earlier history of lues, seemingly properly treated, the single doubtful test together with a number of findings indicating a pituitary dysfunction. Incidentally, the case has cleared up on anterior lobe medication. Under the circumstances there seemed to be no impropriety in including this case in the series.

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*All demonstrated cases of nephritis and gout have been deleted.

The data for the Blood Morphology are given in the next table.

TABLE VI

BLOOD MORPHOLOGY

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Haemoglobin.............Av....	%	**88**	**88**	**94**	**88**
Erythrocytes.............Av....	10^6	**4.94**	**5.01**	**5.36**	**5.00**
Color Index.............Av....		0.89	0.88	0.88	0.88
Leucocytes..............Av....	10^3	**7.9**	**7.8**	**8.5**	**7.8**
P. M. N. Neutrophiles.....Av....	%	**56**	**57**	**64**	**57**
% = or > 75%.............	%	0	5	29	
Lymphocytes............Av....	%	**35**	**36**	**27**	**36**
% = or > 33%.............	%	53	62	43	59
Eosinophiles............Av....	%	**2**	**3**	**1**	**3**
Net % = or > 3%*.........	%	28	31	14	30
Monocytes..............Av....	%	**7**	**4**	**8**	**4**

The general picture is one of normality. The tendency toward a secondary anaemia reported by others (23), (24), (25), (5) has not been observed by us. In fact, the highest values are found in the frank hyperactive cases. Falta (5, p. 274) would seem to regard the reduction as characteristic of the later stages. Later (p. 312) in connection with hypophyseal dystrophy, he observes only a lowering of haemoglobin. Even this deviation does not appear in the present series. Isolated cases, naturally, exhibit some secondary anaemia. Our lowest haemoglobin was 50 per cent and the averages as given above are normal. A slight relative lymphocytosis finds expression in the average value, while nearly two-thirds of the individual subjects show lymphocytes above the conventional normal number. Falta (5, p. 312) makes the same observation on a small number of cases. Our observation has been that where the slightest increase in these cells is not observed, there is apt to be a marked decrease with values for the neutrophiles exceeding the normal. The lymphoid bloods, in our experience, are found with all the endocrine states—and in an appreciable number of non-endocrine conditions.

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* Cases in which a non-endocrine cause of eosinophilia was demonstrated have been deleted.

The other point of significance in the pituitary blood picture is the slight upward tendency of the eosinophiles. This fact has been reported by a number of observers (24), (5, p. 274, 312), (2), (26), and in single cases the observed percentage has assumed most significant proportions. Failure to eliminate non-pituitary causes, at least in the earlier cases, may account for some of these latter. Nearly one-third of the patients show this tendency even after all those demonstrating non-endocrine causes of eosinophilia have been deleted. The combination of an eosinophilia of moderate degree coupled with an increase in the uric acid of the blood, the other constituents exhibiting normal levels, is seemingly peculiar to pituitary disturbances. Such observations play an important part in establishing the general picture, all parts of which are necessary for definite diagnosis.

A most important chapter in the study of endocrine disorders deals with the respiratory metabolism. The data of our observations together with certain other informative concomitant measurements are collected in Table VII.

While the significance of the respiratory metabolism in endocrine disorders has been stressed by many writers, the striking variations produced by aberrant thyroid activity has tended to minimize consideration of the other ductless glands. This is seemingly particularly true as regards pituitary disease, and in the paucity of the published data is found one reason for the conflicting opinions which even today come to expression. Another and even more potent influence tending toward disharmony lies in the classification of pituitary conditions. While acromegaly is initially the result of a state of hyperfunction, the gland certainly may undergo functional involution, and in many cases in the later stages presents a laboratory picture which is the antithesis of that of the initial phase. As far back as 1912, Cushing (2, p. 22) emphasized this point and criticized adversely the findings of earlier investigators who had ignored this most significant observation. The designation of cases as acromegalic without further qualification inevitably leads to confusion. Falta's analyses of the few cases of Magnus Levy (27), of Salomon (28), and of Bernstein and himself (5, p. 276) leads to the conclusion that uncomplicated acromegaly does not increase the basal metabolism, confirming the opinion of his quoted authorities. Confusion of the glycosuria of this condition with diabetes, and the assumption that the latter greatly increases metabolism, is one factor leading to his erroneous conclusions.

TABLE VII

Respiratory Metabolism

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Basal Metabolism Deviation					
High	%	−4	+33	+23	+33
Low	%	−24	−28*	+14	−24§
+ Average	%	−	**+8**	**+18**	
%	%	0	8	100	
− Average	%	**−15**	**−13**	−	
%	%	100	92	0	
% > + 10%	%	0	2	100	
% between +10% and −9%	%	19	34	0	
% = or < −10%	%	81	64	0	
Blood Pressure					
Systolic Av.	mm.	**117**	**113**	**165**	
% < 110 mm	%	27	39	0	
Diastolic Av.	mm.	**72**	**73**	**95**	
% < 65 mm	%	26	23	14	
Pulse Rate Av.	per min.	**72**	**72**	**83**	**72**
% = or < 70 per min	%	43	43	14	
Respiration Rate Av.	per min.	**14**	**15**	**14**	**15**
% = or < 10 per min	%	11	9	0	
Temperature Av.	deg. F.	**98.4**	**98.0**	**98.3**	**98.1**
Alveolar CO_2 Av.	mm.	**40**	**39**	**38**	
% > 35 mm	%	57	67	71	66
% = or < 30 mm	%	5	3	0	3

The slight rise in basal rate observed by Benedict and Joslin (29) in diabetics without emaciation and confirmed by the latter's more extended observations (Joslin, 30), is usually more than compensated by the low nutritional level incident to the condition. This was originally pointed out by Lusk (31), and since confirmed by numerous other observations (32). Benedict and Homan's (33) hypophysectomized dog showed a definite decrease. Snell, Ford, and Rowntree's (34) observa-

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*Complicated by partial inanition.
§Uncomplicated. See Note 1.

tions are scarcely pertinent, as of their seven cases five were of diabetes insipidus, a condition not certainly directly referable to pituitary disorder. Means (35) found a lowered rate in obesity of pituitary origin, an opinion more recently confirmed by others. Boothby and Sandiford (36) analyze thirty cases of acromegaly showing respectively 50 per cent over +10 per cent, 43.4 per cent with the conventional normal range of +10 to —10, and 6.6 per cent below the latter figure. These values equate perfectly with the varying functional level of glandular activity incident to the disease. Less easy to explain are the same authors' report on fifty-eight cases of "hypopituitarism" in which with 53.5 per cent below —10 per cent and 34.5 per cent in the normal range, they report 6.8 per cent (4 cases) with rates above +16 per cent. The warrant for including these latter under the diagnostic caption, is questionable. In the light of the experience of this laboratory they would seem far more probably dysfunctional types in which the anterior lobe still manifested some measure of over-activity. We have had opportunity to study several patients (a typical case protocol is included in the later discussion) over an extended period during which, as the result of their own decision, they remained without treatment. In these, the slow involution of glandular activity has been directly apprehensible, and the terminal phase, a true hypopituitary state with lowered basal rate and greatly increased sugar tolerance. Boothby (37) concludes, however, that "there is very little evidence that the secretion of any part of the pituitary gland . . . acts as a calorigenic agent." A number of other papers might be cited, but they would serve only to add to the contradictory opinions contained in the representative articles discussed above. Analysis of all existing data, irrespective of opinion, would seem to show that an over-activity of the anterior lobe conditions a moderate rise in the basal rate, and that the complementary failure produces an equivalent depression. There is an interesting suggestion of correlation in the facts that the anterior lobe is that portion of the gland essential to life, and that the great majority of cases of pituitary disease presenting well marked symptoms, show a lowered activity of this portion. Even in acromegaly, when the hyper-active phase obtains long enough to produce the striking structural changes characteristic of the syndrome, there is a definite tendency toward a recession of activity to an ultimate hypofunctional end state.

Before turning to the data of the present report it may not be inappropriate to re-emphasize one point. The diagnoses here presented are not the result of a single measurement apparently confirming a series of subjective evidences suggestive of some classic syndrome. They are, on the contrary, based upon a long series of carefully executed tests, the significance of each of which has been thoroughly defined by preliminary studies both with normal controls and cases whose surgical history defined the underlying pathology. These concrete facts were taken as the basis for the interpretation of the equally carefully acquired results of the physical examination and the subjective elements of the medical history. Finally, no one bit of evidence was accepted as indicating endocrine malfunction until every non-endocrine potential cause of such fact had been ruled out by test and observation. Finally the patients have been submitted to the therapeutic test of the indicated medication with observed improvement in clinical condition and laboratory findings. It may seem that undue emphasis is laid on this aspect of the work, but the record of diagnostic contradictions which were a genetic factor of this whole study makes us feel that this consideration is of basic and fundamental importance.

In the table given above it will be observed that the extremes of variation in the uncomplicated cases fall between —24 per cent and +33 per cent. The prevailing downward tendency is shown by the dominant fraction exhibiting values below —10 per cent. In the earlier stage of over-activity there is an unmistakable increase in the basal rate which, as the figures in the present series show, has never exceeded a moderate amount. In the small group of purely hyper-active cases, all adults, there were evidences of acromegaly in every patient. The downward tendency of the blood pressure, as was noted by Cushing in his series, is clearly manifest. Individual cases may fall below a systolic reading of 100, but the tendency is toward a moderate decrease falling short of the levels seen with the other endocrine glands. The seeming hypertension of the over-active cases is probably not due to the well known pressor action. Several of the cases in this group had a complicating cardio-renal condition and, while a specific influence is not definitely ruled out, conservatism would reject it. The fall in blood pressure recorded in the course of acromegaly does not necessarily presuppose an initial hypertension. The average pulse rates are normal—in the hyper-functional group, a little raised—but in the two large groups nearly one-half were below 70. Inspection of a series of cases shows a definite tendency downward, but rarely does the rate assume the low level of the thyroid failure. The respiration rate is seemingly not affected by this nor, in fact, by any of the endocrine glands except the thyroid. A rapid rate can usually be referred to some exciting cause other than the gland function. Body temperature shows normal averages with but moderate departures in the individual cases. Alveolar carbon dioxide shows equally normal tensions. Two-thirds of these cases are above the conventional low normal limit, and only three present a level suggestive of an existing acidosis. To summarize then, the level of functional activity of the anterior lobe produces like deviations of moderate degree in the basal rate. The blood pressure and pulse manifest a downward tendency—exception has already been noted in the pure hyper-functional states—while the remaining observations conform substantially to the generally accepted normal values.

As the respiratory exchange is seemingly controlled by the anterior lobe, so the carbohydrate metabolism is generally regarded as reflecting the functional level of the posterior lobe of the gland. The data for this observation are found in Table VIII.

Before discussing the table, a few points may be explained. First, galactose is the sugar used, for reasons discussed in full elsewhere (38a, b, c, d, e), and the tolerance is determined by the appearance of sugar in the urine, it having been shown by one of us (38b) that the relationship of the dose to this level determines the shape of the so-called diagnostic curve. Further, while the male gonad has no influence on the galactose tolerance, with the female the opposite is the case. Normal tolerance ranges from the twenty grams of the prepubertal girl, through the forty of the adult woman to a post-menopausal level between thirty and forty. Pregnancy produces a lowering, first to thirty and ultimately to the prepubertal level of twenty, returning gradually to the original normal level after delivery. For this reason, the expression of the tolerance dose in grams is misleading, and percentage variations from the individual's normal must be substituted. For the sake of uniformity, a like convention is adopted with the data of the male group.

TABLE VIII

GALACTOSE TOLERANCE

Observation	Unit	Gland Function			Grand Average
		−	±	+	
Male					
Dose.............High......	gms.	70	60	20	
Low.......	gms.	40	5	5	
% above Normal............	%	100	5	0	
Average Deviation of Dose.....	%	+73	+67	—	+70*
% equal Normal.............	%	0	13	0	
% below Normal............	%	0	82	100	
Average Deviation of Dose.....	%	—	−50	−53	−52*
Female					
Dose.............High......	gms.	120	80	20	
Low.......	gms.	30	5	10	
% above Normal............	%	100	5	0	
Average Deviation of Dose.....	%	+74	+80	—	+77*
% equal Normal.............	%	0	2	0	
% below Normal............	%	0	93	100	
Average Deviation of Dose.....	%	—	−53	−67	−60*
Summary					
% above Normal............	%	100	5	0	
% equal Normal.............	%	0	6	0	
% below Normal............	%	0	89	100	
Average + Deviation*........	%	+74	+74	—	+74*
Average − Deviation*........	%	—	−52	−60	−56*

A cursory inspection of the table demonstrates that the pituitary exercises a profound influence on the capacity of the organism to utilize carbohydrate. Examination of the dysfunctional group demonstrates further that the posterior lobe exhibits a tendency toward over-activity as marked as is that of the anterior toward under-activity. The numerical predominance of this group is certainly not fortuitous, as these cases are drawn from a group of nearly two thousand patients submitted for diagnostic study. That the superior limits should exceed the inferior, is to be expected from the numerical relationships. In fact, it is somewhat surprising that they show so close an agreement. The magnitudes speak for themselves and require no discussion. Obviously, the tolerance for galactose offers a valuable diagnostic point.

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* Not weighted for relative number of cases.

With the general differential picture of the three types of malfunction portrayed with certain inherent limitations in the preceding tables, the consideration of certain other pertinent matters not susceptible to tabular analysis may next claim attention.

PART II

In spite of the important advances that have been made in our knowledge of the pituitary gland during the past ten years, there is still much ignorance in regard to it, and especially in regard to the effect of disturbances in its function as contrasted with the results of tumor growth involving the organ upon bodily nutrition and metabolism. Due largely to the work of Cushing (39) and his collaborators much more is known concerning ''surgical'' pituitary disorders than those not demanding operative intervention.

This lack in regard to functional disturbances is due largely to the fact that, acromegaly excepted, there has been no certain method of establishing the diagnosis of disturbed pituitary function in any individual patient save by surgery or autopsy, and a painstaking analysis of cases in which the diagnosis was in many instances uncertain has not appealed to those to whom abundant material was available.

This paper comprises an analysis of clinical and laboratory findings in a series of patients in whom the diagnosis of pituitary malfunction seems reasonably established by clinical symptoms, laboratory findings, and the progress of the condition while under observation. The laboratory data are based on an analysis of 400 cases; the clinical findings embrace only one hundred.

There are several reasons for choosing this smaller number of cases for clinical analysis. First, all the patients in this smaller series have come under the immediate observation of one of us (C. H. L.) so that there has been a fair chance properly to evaluate the symptoms and signs presented; second, the number seems sufficiently large to permit reliable conclusions; and third, it is the same as the number of acromegalics and patients with pituitary tumors recently reported by Davidoff (40) and Frazier and Grant (41), respectively.

In contradistinction to their patients all of those comprising the clinical section of this paper had hypofunctional disturbances of the pituitary, that is, either hypofunction of both lobes, or that condition described by Cushing (39), in which the anterior lobe is underactive while the posterior lobe is either normal or overactive. Inasmuch as it is impossible to distinguish between these conditions clinically, they are all grouped together in this analysis.

CLINICAL FINDINGS

In tabulating our clinical findings an attempt has been made to follow the plan used by Davidoff (40) in order that a comparison of findings might be easily made. Such a comparison brings to light very important points of difference and similarity between the two groups.

Incidence

Functional disturbance of the pituitary other than that caused by tumor of the gland is considered by the majority of physicians to be a rare condition, and important more as an interesting curiosity than as the cause of important disturbances of body function. This was our own point of view at the beginning of this study, but as our method of diagnosis has become more reliable, we have found that the pituitary is no more immune to disturbances of function than is the thyroid or the pancreas—its humbler position in medical thought is due not to its relatively infrequent involvement, but to the fact that this often exists unrecognized. In a series of 1000 cases examined in our clinic, 65 per cent have been found to have definite and significant disturbances of metabolism of endocrine origin. Of these, 12 per cent have presented symptoms and laboratory findings diagnostic of thyroid hypofunction; 14 per cent of ovarian dysfunction; 1.3 per cent of Addison's disease; while 28.4 per cent have been classed as disturbed pituitary function.

On the basis of these figures we are forced to the conclusion that disturbance of pituitary function is more common than is generally appreciated, but that the cause of symptoms produced by early or moderate disturbances is not generally recognized. Unless the patient exhibits definite acromegaly, giantism, or marked obesity of the pituitary type, the possible connection of hypophyseal function with the syndrome is usually not even considered. Yet Davidoff states that "the surgically verified cases also show that hypophyseal adenomas *without* acromegaly are about five times as frequent as those *with* acromegaly." If adenomata of the pituitary gland produce their most characteristic symptom only once in six times, it is not illogical to believe that disturbances in its function may often be present without giving rise to so-called pathognomonic symptoms, which allow a tentative and tenuous diagnosis to be made by inspection. Our conclusion concerning the incidence of disturbed pituitary function in so far is supported by proven facts.

Race. All the patients in this service were members of the white race, as were Davidoff's. Beyond this our analysis does not go, as the birthplace of the patients was not recorded, and in these days of wholesale immigration it is impossible to determine the nationality of a patient by the character of his patronymic. Our impression is that the majority were born in America, and that of those whose names were diagnostic the largest number of patients of foreign extraction were Jewish. This may be due to the population from which the majority of our patients come, or to a real susceptibility of the Jewish race to endocrine instability.

Sex. In our series there were 68 females and 32 males. At first sight this does not seem to agree with the findings of other observers (42) (43) who find acromegaly, at least, equally distributed between the two sexes. In Eidelsberg's (44) series of cases of hypopituitarism, however, the distribution was 55 per cent females and 45 per cent males. Reference to our larger series shows a predominance of males in the hyperfunctional, a preponderance of females in ratio of 2 to 1 in the dysfunctional and nearly 3 to 1 in the hypofunctional groups. The preponderance of females in our series is doubtless due in some part to the fact that men find it more difficult to take time for hospitalization, so long as their illness is not incapacitating. Another factor may exist in the type of the disorder.

Age. The age of the patients at the time they entered the clinic is given in the following table:

TABLE IX

Age in years	Number of patients
1-10	2%
10-20	30%
20-30	22%
30-40	17%
40-50	20%
50-60	8%
60-70	1%

The extremely low figure for the first decade is undoubtedly unreliable. Metabolic studies on young children require special apparatus and special cooperation on the part of the patient. Undoubtedly the figure would be higher were we able to study satisfactorily all the children under ten years of age who present themselves at the hospital. It is significant, however, that between ten and twenty years are noted the greatest number of patients. Undoubtedly this is due to the fact that puberty occurs in this decade. In talking with these patients one is impressed with the large number who connect the beginning of their complaint with puberty, and the undoubted increase in endocrine activity during that epoch is an important factor in activating a potential functional weakness of the pituitary. The importance of its integrity for normal sexual development is well known, and our figures serve only to accentuate the fact that puberty is an important factor in changing a potential pituitary failure into an overt form. The sudden drop in incidence in the sixth decade also suggests the intimate association of the pituitary and sex functions.

An attempt to determine accurately the age of onset of symptoms in our series was unsuccessful, because of their gradual nature and the tendency of patients to connect their complaints with some manifestly unimportant event. Puberty, or its absence long after it should have occurred, was the most common single datum obtained.

The next largest group, all women, dated the beginning of their complaints from the birth of their first baby, irrespective of their own age, while a somewhat smaller number presented themselves because of sterility. It is manifestly impossible to determine the duration of complete sterility unless one concludes that it existed from birth, or earlier. The significant fact is the large number of patients in whom pituitary malfunction is connected in some way with demands for increased activity due to some phase of the sexual life.

Occupation. No important relationship between occupation and pituitary disturbance could be detected.

FAMILY HISTORY

In only one case was there a definite history of acromegaly in a near relative. In ten cases there were one or more instances of abnormal height in near relatives. In eight cases there was a story of family obesity similar in distribution to the patient's. Nine patients gave apparently reliable stories of diabetes in near relatives. In three per cent, thyroid disorders appeared in the history of the immediate family, and in seven per cent there was the statement that some near relative had had "gland trouble." The significance of this last statement is open to question, but exclusive of that number, and of those with a family history of obesity, there is a history of definite endocrine disorder in some near relative in twenty-three per cent of our patients. As in diabetes (45) and thyroid disorder [see Janney (7)] there is evidence that the integrity of pituitary function is subject to inheritable factors.

MARITAL HISTORY

Only fifty-five per cent of our patients were married. This figure is much lower than Davidoff's. If, however, we exclude those below twenty years from our calculation, the figure will be raised to eighty per cent, which is not significantly different from his. We are inclined to agree with him that this small number of marriages is due in considerable degree, to the blighting effect of pituitary malfunction on gonadal activity and sex life.

Of the productive marriages, the resulting number of children was one in 28 per cent, two in 23 per cent, three in 31 per cent, and four, five, and six in 6 per cent each. In this group of patients who were not sterile the pituitary disturbance, so far as could be determined, did not antedate the pregnancies.

To summarize, only 55 per cent of our patients were married, 36 per cent of those married were sterile, and an additional 28 per cent had less than the normal average number of children, convincing evidence of the importance of disturbances of pituitary function in influencing fertility. Were we certain of the potency of the patient's mate in each marriage and of the relation of beginning of symptoms to the date of marriage in every case, the figures would be still more significant. A study of sterility is now being carried on in our clinic which we hope will contribute important information on this question.

PAST HISTORY

Development. Eighty patients gave histories of normal physical and mental development. This coincides nearly with Davidoff's figure for acromegalics (40). In 13 per cent there was a history of significant early obesity or abnormal skeletal growth. Seven per cent had had difficulty in keeping up with children of their age in school. None of these figures is particularly significant, and the criteria are unsatisfactory. No conclusions can fairly be drawn from them. Much more significant are the findings in regard to puberty. Of 92 patients beyond normal puberal age, delayed or absent sexual development was present in 32, almost 35 per cent. Of these, two were males, thirty were females, although of the entire group thirty were males and sixty-two females. In other words, nearly 50 per cent of the female patients and only 6 per cent of the male patients beyond the normal puberal age showed delayed sexual development. It is, of course, far easier to determine accurately the onset of maturity in the female than in the male, and it is probable that the apparent low percentage of delayed sexual development in males is to some degree explained by the lack of a definite symptom. It would hardly account, however, for the entire difference in the figures. Here is a question which demands further investigation.

The answer may lie in the greater susceptibility of females to endocrine disturbances in general, and it is possible that this susceptibility is due to the fluctuating endocrine balance associated with menstruation and pregnancy. The apparent demonstration by Frank (46) of the appearance and disappearance of a female sex hormone in the circulating blood is of possible significance in this connection.

Previous Illnesses

The incidence of previous illnesses in our series of patients is shown in the following table:

TABLE X

Past History

Operations	57%	40%—removal of tonsils and adenoids 8%—appendectomy. 9%—miscellaneous.
Trauma	7%	2%—involving head. 5%—other parts.
Scarlet Fever	19%	
Typhoid	7%	
Pneumonia	7%	
Influenza	19%	
Tonsilitis	58%	
Meningitis	5%	
Mumps	37%	
Miscellaneous	12%	3%—rheumatic fever 3%—sinusitis. 3%—tuberculosis. 3%—malaria.
Relation to Present Illness		Definite 1%—pregnancy. Possible 4%—infections. Not established—95%.

Two significant facts appear in this table: one, that the onset of the condition is so gradual that only 5 per cent of patients can connect it in any way with preceding illness; the other, that there is an extremely large percentage of definite focal infection in these patients. Even discounting the present enthusiasm for removing tonsils, the fact that 40 per cent of our patients had had tonsillectomy cannot be easily dismissed. Appendectomy is an operation concerning which there is little hesitation at present, yet the table shows only one appendectomy for each five tonsillectomies. The incidence of tonsils so diseased as to demand removal must, therefore, be accepted as significant.

In this connection, the figures for tonsillitis are confirmatory and significant. Only patients who had had frequent and repeated attacks of "sore throat" are included in the 58 per cent charged with tonsillitis, yet the incidence is significantly greater than that of mumps, a common disease of childhood, easy of identification. The conclusion may fairly be drawn therefore that tonsillar infection and disturbed pituitary function coexist in a significantly large number of cases.

The question as to which condition causes the other is as yet not definitely answered, but observation of our patients after removal of diseased tonsils strongly suggests that focal infection is in many associated with the depression of the glandular activity. The following case is significant.

PROTOCOL 1

The patient was a tall, thin school girl, 17 years of age, presenting amenorrhea as her chief complaint. The menses had never been established and she had always been below her predicted weight. During the past year she had grown very rapidly.

The family history is without significance, except for a paternal aunt who did not menstruate until after her sixteenth birthday.

The patient's past history records only a few minor ailments in childhood and a mild attack of influenza in 1920. But for her present difficulties, the general level of her health has been excellent.

Physical Examination: The patient was a tall, very thin, moderately nervous girl, intelligent and co-operative; with a height of 67 inches in her shoes and a weight of 92½ pounds in her underwear. The skin and mucous membranes were somewhat pallid. The teeth showed evidence of much dentistry. The tonsils were large and scarred and the pillars injected. She had infantile breasts; there was neither pubic nor axillary hair, and examination by the rectum showed an almost infantile uterus. The pulse was slightly high and the blood pressure definitely low.

Laboratory Examination: The urine was practically normal, except for a very slight trace of albumin. The blood showed 75 per cent haemoglobin, normal erythrocyte count, a slight leukopenia and a substantially normal leucocytic formula. The smear showed a moderate achromia. Blood chemistry showed a low non-protein and urea nitrogen and high uric acid a blood sugar value of 120, a value probably above the truth. The basal rate was reported as identical with prediction. This value was undoubtedly high.

Comment: The delayed menarche, absence of breast development, and body hair, the small uterus and the patient's body configuration are typical of hypophyseal infantilism. Pelvic examination under anæthetic confirmed the findings by rectum, and eliminated other pelvic disorder.

Treatment and Progress: The patient was given pituitary extract, anterior lobe, beginning with 8 grains daily and rapidly increasing to 16 grains. Tonsillectomy was advised but refused.

On January 15, 1925, her weight was 108¼ pounds; hemoglobin, 90 per cent; blood pressure, 100-70. The breasts had developed a little and there was a slight growth of axillary and pubic hair. A week ago she had severe cramps in the pelvis, lasting 8 hours, the breasts being sensitive at that time.

On June 10, 1925, her weight was 113½ pounds. She had not menstruated, but the breasts were now normal in size and the pubic and axillary hair normal in amount.

On December 3, 1925, her weight was 115 pounds. Her general health was excellent, with no menstruation or molimina.

June 24, 1926. Four days ago menstruation began and persists. She was feeling well. Her weight had increased to 119½ pounds. Her height was 69½ inches. The basal metabolic rate was —4 and the pulse rate 72.

July 15, 1926. The gynaecologist reports that the uterus is much larger, being practically normal in size.

January, 1927. The patient reports having had one short period, and one attack of pelvic cramps lasting 12 hours.

Tonsillectomy was performed in March, 1927.

June, 1927. The patient reports another menstrual period, of normal character. She complains of frequent frontal and vertical headaches, beginning about four weeks ago. At the same time, there is occasional mild vertigo. She is advised to diminish the dose of pituitary extract to 10 grains daily.

December, 1927. Menstruation has continued regularly since June. The headache disappeared when medication was diminished. she reports herself in perfect health.

Comment: The interesting features in this case are: First, the response to oral pituitary medication; and, second, the effect of removing focal infection. The idea that pituitary extract is not effective when given by mouth is, we believe, unjustified. Undoubtedly, the dosage usually employed is insufficient, and in certain patients even large doses produce no typical results. Focal infection is a probable factor in many cases showing negative results. Conditions within the digestive tract possibly interfere with absorption in others. The possibility of success is, however, great enough to justify treatment by oral medication, provided one is prepared to push the dosage if necessary, and to remove any inhibiting factors which exist in the individual patient. The whole question of endocrine medication will be considered at length in a series of papers now in preparation.

The permanent establishment of menstruation following removal of the tonsils, together with the simultaneous appearance of headache relieved by diminishing the dose of pituitary extract can only be interpreted as indicating an improvement in pituitary function when the focal infection was eliminated. It is our belief that focal infection, especially of the tonsils, is a definite etiological factor in pituitary hypofunction. No other significant relationship appears in the table.

THE EXISTING CONDITION

One can hardly use the term "disease" in relation to departures from health due to disturbed function without definite organic change. The majority of our patients were able to "carry on" in spite of their handicaps, but their lack of health was sufficient seriously to interfere with their efficiency and enjoyment. The symptoms and signs as recorded in the clinical histories, are tabulated below.

TABLE XI

Symptoms and signs as recorded in clinical histories:

Symptom	*Incidence*
Enlargement of acral parts	6%*
Enlargement of sella turcica on x-ray examination	5%
Disturbance of menstruation	51%†
Headache	34%
Complete amenorrhoea	8%‡
Visual disturbances	7%
Excessive perspiration	3%
Hypertrichosis	28%
Drowsiness and lethargy	8%
Changes in weight (greater than ±10%)	73%
Diminished libido	11%
Asthenia	36%
Low blood pressure (less than 120 mm. Hg.)	28%
Paraesthesias	20%
Polyphagia	4%
Polydipsia	1%
Constipation	29%
Vomiting (with present illness)	10%
Rhinorrhoea	1%
Photophobia	1%
Uncinate attacks	3%
Failing memory	1%
Decrease of body hair	0%
Persistent lactation	1%
Failure of breasts to develop	1%
Epistaxis	0%
Choked discs	3%
Vertigo	14%
Tinnitus	17%
Deafness	15%

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*Definite acromegaly.
†Of females over 14 years of age.
‡Of females over 14 years of age.

A comparison of the above findings with Davidoff's table of symptoms (40) shows certain interesting similarities and differences. Those symptoms which are in all probability due to disturbed nutrition show a strikingly similar incidence in both tables; those due to enlargement of the sella, present in large numbers in his table, are rare in ours.

Enlargement of acral parts appears, at first sight, to be an exception to this rule. Davidoff, however, studied only patients having such enlargement, while our study comprises all types of disturbed pituitary function. Moreover, we have excluded from our table many patients in whom disturbances of acral growth, or asymmetry of development was definitely present although there was not the facial distortion characteristic of acromegaly. If we were to include in our table all those patients who showed asymmetrical skeletal growth, the figure would be greatly increased. From the diagnostic point of view, bodily asymmetry is one of the most important stigmata of disturbed pituitary function, past or present.

Distortion of the sella demonstrable by x-ray was absent in all but 5 per cent of our patients. This is, of course, no evidence concerning the function of the pituitary. Disturbance of its function may exist without affecting the sella outline and an abnormal sella shadow does not prove that the pituitary is in any way involved. This fact has been emphasized by Camp (47) and is well illustrated by the following case.

PROTOCOL 2

The patient was an English woman, 44 years of age, who was referred because of severe headaches. During the past twenty years these have occurred at fortnightly intervals. The pain starts suddenly, is severe and throbbing, and usually begins in the frontal or temporal region, later extending to the vertex. The pain lasts from one to three days and ends spontaneously and abruptly. During its course nothing affords relief. There are no associated disturbances, neither nausea, vertigo nor visual aberration. Eight years ago drainage of one maxillary antrum was performed in the hope of affording some relief. Following this, there was freedom from pain for about six months. At that time the patient had an attack of influenza, subsequent to which the headaches returned and have persisted to the present, gradually increasing in frequency and severity.

Family History. The father died of pneumonia at the age of 36; the mother of arteriosclerosis at 64. Four sisters and one brother are living; one sister has died of cancer. All members of the family are abnormally tall.

Past History. The patient reports several minor ailments and scarlet fever in childhood. She was undersized until 16 years of age, and then grew rapidly for the next two years, attaining her present height of 5 feet 7 inches. She had rheumatic fever at 18, and influenza as above noted. The catamenia was established at 16 and has apparently been perfectly normal.

Physical Examination shows a tall, somewhat emaciated white woman with prominent lower jow. Beyond infected tonsils the findings were normal.

Laboratory Examination. The general urine picture was normal, except for one specimen showing a trace of albumin. The blood showed a slight relative lymphocytosis, but was otherwise not significant. The blood analysis gave low normal values for all the nitrogenous constitutents, with a normal blood sugar. The basal metabolic rate was —4 per cent. The patient was 20 per cent under weight. The blood pressure shows a mild degree of hypertension. The sugar tolerance is normal, as are the eye findings. Radiography of the skull showed a large deep sella (Plate 1), and a slight thickening of the membranes lining the maxillary sinuses. On the basis of the appearance of the sella a diagnosis of slow growing pituitary tumor had previously been offered.

Comment. Although the x-ray findings suggested a pituitary tumor, the patient's general condition and more definitely the normal laboratory examination and eye findings failed to support such a diagnosis. The x-ray also disclosed infected sinuses, and these were operated upon successfully, but a mastoiditis developed as a sequel. Since her recovery from this latter condition she has had no more severe headaches, the condition being confined to a rare mild attack of brief duration.

Note. If a diagnosis of pituitary tumor on the radiographic findings of the sella is ever justifiable, the picture presented in this patient would seem to be an ample warrant. The laboratory examination, however, was wholly negative, and, more significantly, the result of treatment would seem to indicate a purely non-endocrine cause of the patient's difficulty. We do not feel that a single observation of this type ever forms a firm basis for a diagnosis, and that the carefully compiled history and physical examination, supplemented by complete metabolic studies cannot be supplanted by any single observation.

In a study of pituitary function, radiography of the sella turcica is valuable because it helps to establish the presence or absence of tumor, not because it affords any information concerning functional disturbance.

Of much greater importance, we believe, is the evidence gained by a complete study of the eye grounds and visual fields. This was done, in our patients, by Dr. W. D. Rowland, to whom our thanks are due for his most important contribution to this study. His findings in 84 cases are tabulated in Table XII

The importance of studies of the eye in pituitary disturbance has been emphasized in a recent article by Frazier and Grant (41). We have found it of enormous value both in establishing the diagnosis of pituitary disturbance, and in separating the cases in which tumor is present from those in which there is no growth. Even in the latter group contraction of the visual fields is not uncommon, and definite enlargement of the blind spots is the rule rather than the exception. The character of the contraction of the visual fields frequently leaves little doubt that they are due to the pituitary condition, especially as sinus disease has been ruled out in our patients. Whether the blind spot enlargement is due to pressure from a pituitary which is slightly enlarged or to nutritional changes is not so certain, but from the point of view of diagnosis this finding is extremely important. The lack of subjective visual disturbances is no evidence that the visual fields are normal for we have seen a considerable number of patients with markedly contracted fields who stated that there was no difficulty with the vision. That such contractions may be caused by simple hyperplasia or functional disturbance of the pituitary is evident from the work of Finlay (48), Erdheim and Stumme (49) and Carvill (50).

TABLE XII

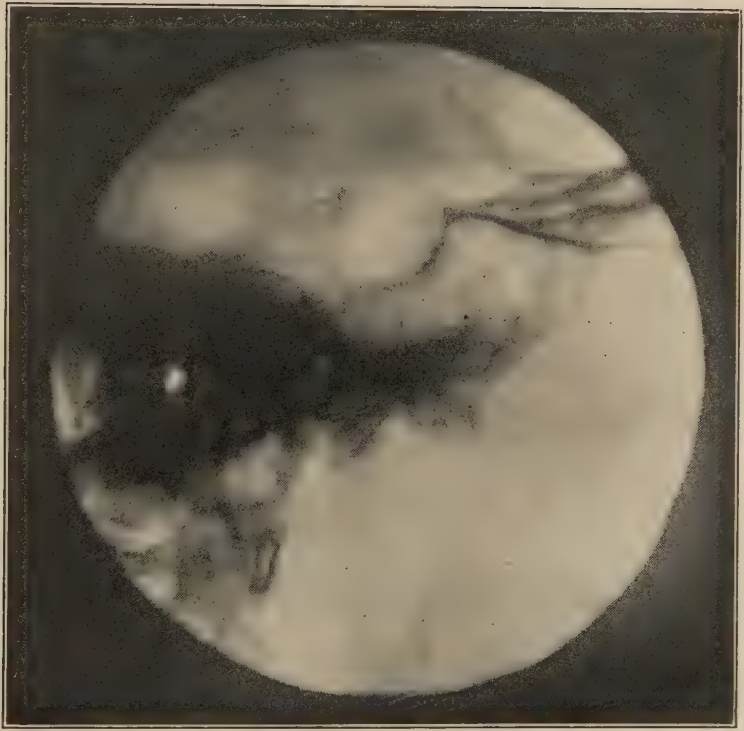
Eye Findings in Eighty-four Cases

Choked Discs	3%
Yellow Discs	19%
Hazy Discs	10%
Optic Atrophy	1%
Vessels Sclerosed	3%
Contracted Visual Fields	29%
Enlarged Blind Spots	64%

Disturbances of the Menstrual Cycle. Fifty-nine per cent of our female patients showed disturbance of menstruation, if we consider those adults in whom menstruation was entirely absent with those in whom it was present but abnormal. In four of our patients with amenorrhoea, menstruation had never appeared, and examination showed juvenile pelvic organs. In four others, menstruation had been established for varying periods and the pelvic organs were not demonstrably abnormal.

The disturbance of the menstrual cycle in our series was characterized by late menarch, short duration of catamenia and scantiness of flow, increased intermenstrual interval, and ab-

PLATE 1



Case B-412. X-ray of sella showing probable tumor. Patient gave no evidence of functional pituitary disease.

sence of significant pain. These changes in menstrual behavior are, we believe, characteristic of an associated pituitary hypofunction as contrasted with other endocrine disturbances. Menstruation may be markedly disturbed by abnormal thyroid function, but in that condition menorrhagia and shortened intervals are as common as the reverse, while in ovarian hypofunction pain is commonly a prominent symptom. The group of disturbances mentioned above, especially if found in a patient with asymmetrical physical development demand a careful study of the functional level of the pituitary.

Weight Disturbances. In this series 73 per cent (65 per cent in the larger series) of the patients showed a variation from normal weight, as calculated by the West and Dreyer Standards, of more than 10 per cent. This difference is not necessarily pathological, but forms a fair basis for classification. Of those whose weight was not normal, 57 per cent were overweight. Underweight was found chiefly in adolescents showing the Levi-Lorain type of disturbance, and seldom amounted to more than —20 per cent, the maximum deficiency recorded being —30 per cent. Overweight while by no means limited to adults, was more common among those over twenty, and was of more marked degree. As a rule overweights of 40 per cent were not uncommon, and the maximum in this group was 60 per cent. The obesity showed almost without exception a predilection for the middle third of the body, the neck, wrists, and ankles remaining nearly normal. Characteristically, these patients gain weight very rapidly, and under certain conditions lose it rapidly, only to regain it again. The obesity is stubbornly resistant to dietary treatment, it being usually impossible to reduce weight and keep the patient well at the same time. It seems logical to suppose that the obesity is connected with the disturbed carbohydrate metabolism of these patients, and from a practical point of view, rigid curtailment of carbohydrate intake is more effective than general reduction of calories in combating this type of obesity.

Besides the definite tendency to abnormal weight, our patients showed clearly the effect of pituitary activity on skeletal growth by the number above "normal height." Of those who had passed the growth period, 25 per cent of the males were over 6 feet, and 18 per cent of the females were over 5½ feet in height. The definite upper limit of normal height is difficult to fix, and these figures are given merely to make clear the definite tendency to increased height in these patients. Not only was their height above the average, but in the majority there was a history of very rapid growth during a limited period of time, most often coincident with or shortly after puberty. Such rapid growth, as well as the abnormal height, must mean a glandular hyperactivity at the time of their occurrence, and we believe that in many of our patients this hyperactivity preceded the state of hypofunction which existed when they were studied. Certainly neither symptom furnishes any valuable evidence concerning the state of pituitary function when the patient comes for examination—they merely suggest that at some time there has been a hyperactivity of the gland. This may still be present, or function may have returned to normal, or have swung still further into the hypoactive phase.

The Skin. The most frequent cutaneous abnormality encountered in our series was hypertrichosis, which was definitely present in 28 per cent, mostly women. Abnormal loss of hair was not present in any of our patients, if we except absence of body hair in the cases of delayed puberty. The changes in the hair consist in altered quality and distribution. The hair of the head, axillae and pubis is thick, oily, and vigorous, and there is a marked tendency toward increased hairiness of the trunk and limbs, most striking in women, in whom hair is usually not found in those sites.

Other than the hypertrichosis, 23 per cent of our patients are described as having some cutaneous abnormality such as roughness, dryness, or excessive oiliness. Cold skin, so common in hypothyroidism, was not noted. Neither were definite eczemas, which are also common in hypothyroidism. Vasomotor instability, frequently encountered in patients with depressed ovarian function, was conspicuous by its absence.

The teeth which might be expected to participate in disturbance of nutrition affecting the hair and skin, were described in definitely abnormal in 28 per cent of our patients. The variations from normal were rapid and general decalcification, malposition, or delayed eruption. The two latter conditions were always associated with other signs of delayed development, while decalcification was present in the obese patients with increased tolerance for sugar. The exact relation of carbohydrate and calcium metabolism is not known, but our findings bear out the idea held by many dentists, that the teeth of individuals who consume large amounts of sugar are usually soft.

The Thyroid Gland. Twenty-three per cent of our patients showed symmetrical, elastic enlargement of the thyroid gland. All of them had basal metabolic rates below normal. For a complete discussion of thyroid enlargement in pituitary disease the reader is referred to the recent paper of Cushing and Davidoff (51). As yet the interrelation of the two conditions is not understood, and a discussion of theories must be omitted here. The important fact from our point of view is that thyroid enlargement and low basal metabolic rate do not always mean hypothroidism, and do not, therefore, always demand treatment with thyroid extract.

The Tonsils. Attention has already been directed to the seemingly important role played by tonsillar disease in pituitary malfunction, as judged from the clinical histories. The physical findings in our series lend confirmation to the idea already expressed, for in only 25 per cent of the patients were normal tonsils present. Forty per cent had had their tonsils removed, and in an additional thirty-three per cent the tonsils, in the examiner's opinion, were definitely infected. The criteria for this judgment were the presence of injection of the tonsillar pillars, with large or irregular tonsils from which pus could be expressed. Tonsils which were merely large or irregular, without injection of the pillars and yielding no pus on pressure, were not termed infected.

The Heart. Neither in the histories of the patients, the physical examinations, nor the electrocardiograms were there any evidence of organic heart disease in this group of patients. This is extremely interesting because of the high incidence of the tonsillar infection, the cause of so much organic disease of the heart. Moreover, in sharp contrast to derangement of the thyroid function, in which functional cardiac disturbances are so common, symptoms of such conditions were conspicuous by their absence. Tachycardia was not noted in the series. Only two patients complained of palpitation, slight in amount and not caused by exercise. Bradycardia was rarely encountered, even in the patients with low basal metabolic rates. This is an interesting and important point, since in thyroid failure the pulse rate usually follows the metabolic rate downward. The fact that it does not do so in pituitary failure suggests that the bradycardia in hypothyroidism is not due solely to the low metabolism, and furnishes evidence of some importance in the clinical differentiation of the two conditions.

The Blood Pressure. Hypotension was much less marked in this series than in hypothyroidism. As a rule the pressures were within or near normal limits under ordinary conditions. Those tabulated in the first section of the paper were taken under basal conditions.

Other Viscera. Only two patients in our series showed evidence of pulmonary involvement. One had a thickened pleura following pneumonia, the other had tuberculosis. No evidence of disease of the abdominal viscera was found in the entire series.

Neurological Findings. Headache was the most common neurological symptom in the group, being present in 34 per cent of the patients with more than occasional frequency. It was usually described as frontal or vertical. So-called ''migraine'' was not common, in contrast to the findings in thyroid failure. Of the 34 patients with headache 25, or 73 per cent, showed yellow or hazy discs and enlarged blind spots, and 32 per cent contracted visual fields, but no papilledema or other evidences of increased intracranial pressure. This close association of headache and eye changes indicate that both are due to a common cause. In the absence of papilledema or contracted visual fields pressure by the pituitary can be eliminated as a factor and the most probable explanation lies in the disturbances of nutrition, characteristic of pituitary malfunction, and their effect upon nerve tissue in general.

That the entire nervous system shows evidence of disturbed function in conditions of abnormal pituitary function is shown by the work of Cushing (2), Davidoff (40), and others, and by the further neurological findings in our series.

Parasthesias. Twenty per cent of our patients complained of numbness and tingling of the extremities—symptoms common to other diseases in which nutrition is disturbed, i.e., diabetes mellitus, and pernicious anaemia. Ten per cent showed definite sluggishness of one or more reflexes, one case showed ataxia, and one, with thyroid enlargement, exhibited a fine tremor of the hands. All these disturbances are apparently the result of imperfect nutrition of the nervous system, as no other explanation fits the facts so well.

Deafness. Deafness has not been emphasized in connection with pituitary disturbances, but 15 per cent of our patients had definite hearing loss, as determined by the audiometer. In 5 per cent, catarrhal conditions could not be eliminated as a possible cause for the deafness, but in the remaining 10 per cent no catarrhal condition could be demonstrated, and the history was typical of the progressive non-catarrhal type—so-called otosclerosis. In the light of the known relation of that disease to pregnancy, and of our knowledge of pituitary function during and after pregnancy, the question arises as to whether otosclerosis is anything more than a nutritional disturbance of the auditory apparatus, brought about by metabolic changes, for some, though by no means all, of which the pituitary may be responsible. Work on this problem is going on in our clinic at the present time and seems to offer hope of the solution of a part, at least, of this baffling problem.

Treatment. It is generally believed that pituitary substance, administered by mouth, is inert. In our experience, this is not entirely true. In ordinary doses, no effect could be demonstrated in the majority of our patients, but doses of from one to two grams (15-30 grains) produced demonstrable results in a large number of individuals. The recent work of Menninger (52), demonstrating that in certain individuals epinephrine is effective given orally, reopens the whole question as to the effectiveness of endocrine preparations thus administered. It may be that variations in the gastric secretion of individual patients account for the variations in the effect of the preparation administered (53). Work is now being undertaken in our clinic to clear up this point, and the results of treatment will be discussed more fully in a later paper.

PART III

Case Protocols

The cases have been grouped according to characteristic symptoms. Typical laboratory data are assembled in tabular form to conserve space.

TABLE XIII

Observation	Blindness		Deafness	
	Number B-70	Number B-71	Number B-130	Number B-238
Diagnosis . . . Anterior	–	–	–	–
Posterior	+	+	+	+
Sex	Female	Female	Male	Female
Age (yrs.)	25	49	53	29
Height (cm.)	159	153	178	155
Weight (kgm.)	37.5	63.7	62.3	48.0
Weight Dev. (%)	–30	+29	–10	+8
Lung Volume Dev. (%)	–28	–26	±0	–25
Basal Metabolism Dev. (%)	–25	–12	–24	–18
Pulse (per min.)	64	72	52	70
Blood Pressure (mm.)	116/80	154/84	102/68	112/66
Temperature (deg. F.)	98.4	98.0	97.8	98.2
Alveolar CO_2 (mm.)	41	41	45	40
Urine Volume (c.c.)	1980	870	910	1370
Spec. Grav.	1.008	1.025	1.028	1.010
Albumin	+	0	0	+
Casts	+	0	+	0
Sugar	0	0	+	0
Total Nitrogen (gms.)	4.62	20.88	12.22	5.16
Residual Nitrogen (%)	3.1	13.1	3.6	9.2
"Urobilinogen"	0	0	+	0
Phen. Sulph. Phth. (%)	47	61	63	89
Gal. Toler., Deviation (%)	–75	–50	–33	–50
Non-Protein Nitrogen (mgm.)	35	38	47	32
Uric Acid (mgm.)	6.3	5.5	4.5	4.1
Sugar (mgm.)	76	84	83	87
Haemoglobin (%)	80	90	95	80
Erythrocytes (10^6)	4.21	5.51	5.95	4.22
Leucocytes (10^3)	5.95	7.20	6.05	6.15
Lymphocytes (%)	45	35	40	45
Eosinophiles (%)	5	4	2	1

BLINDNESS

CASE B-70. The patient's chief complaints were partial blindness (chiefly in the left eye), headache, amenorrhea, and mental depression. Four years ago she began to have headaches, which gradually have increased in severity and frequency, and a few months before her admission necessitated suspension of work and later admission to a hospital. The eye condition came on gradually, but during the recent period of examination there have been intense pain, photophobia, and marked further loss of vision. The mental phase has been intermittent throughout the four years and has intensified with the present illness. The patient matured at 16; the catamenia was regular and scanty up to four years ago. The periods then became irregular with increasing interval, and ceased entirely four months ago.

Family History: Both parents died of pulmonary tuberculosis, and one sister has recently recovered from it. A brother died at seven of meningitis and hydrocephalus.

Past History: Several minor ailments and diphtheria in childhood were recorded. She had influenza four years ago. There is a history of some deafness, pain in ears and tinnitus. The use of glasses earlier gave slight relief to the headaches. She has hacking cough, with expectoration. She has always had some nausea, followed during past few months by occasional vomiting.

Physical Examination shows an under-developed, poorly nourished white female of 25. The left eye is practically blind and with some nystagmus. The lungs show dullness in the apices and fine rales.

Laboratory Summary: The patient is much under weight and her lung capacity is diminished. The basal metabolic rate is —25 per cent; the urine volume is ample, with albumin and casts both present. Protein intake is inadequate for maintenance; residual nitrogen is normal. The galactose tolerance is 75 per cent below prediction. The blood uric acid is very high, with normal non-protein nitrogen. She has a slight secondary anæmia, lymphocytosis (45 per cent) and eosinophilia (5 per cent).

Neurological Examination shows positive Romberg, normal gait, inco-ordination of upper extremities; lesion of second pair and possible eighth nerve involvement.

Eyes: The left pupil does not react to light or accommodation. The right fundus shows papilledema (1 mm.); the left, small, superficial hemorrhage on the nasal side of the disc; the discs are yellowish. The right form fields are normal, the color field contracted; on the left, only a small upper nasal field remains (see plates). The right blind spot is somewhat enlarged; the left could not be delineated. The findings indicate an intercranial growth and lesion in left optic nerve at or in front of the chiasm.

X-Ray: The sella appears to be normal. Infilteration with calcification of the left lung are evidenced.

Ears: No abnormalities are detected. The Barany test gave normal results.

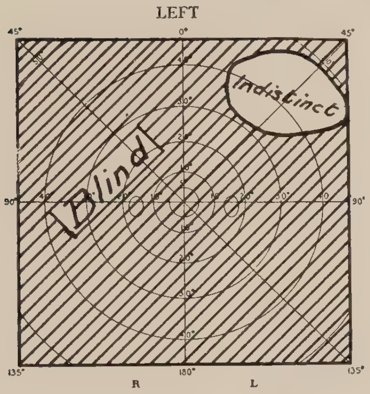
A *diagnosis* of pituitary dysfunction, with anterior lobe under- and posterior lobe over-active, coupled with pulmonary tuberculosis, was established. Because of the latter condition, operation was deemed inadvisable and anterior lobe *medication* was administered in the hope that normalizing the hypo-active portion of the gland might influence favorably the over-active fraction.

Outcome: The patient showed steady improvement and nine months later the eye findings were substantially normal (see plates) with 10/10 vision in the right and 10/12 in the left eye.

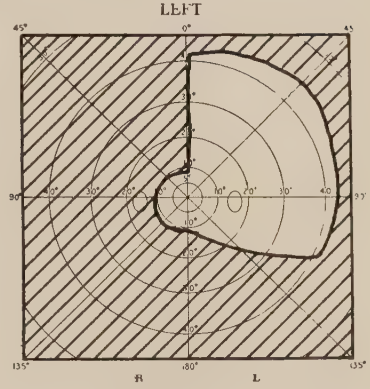
She was discharged to undergo treatment for the tuberculous condition. Three years later she reported with the pulmonary condition arrested. The eye examination showed nothing abnormal ex-

PLATE 2

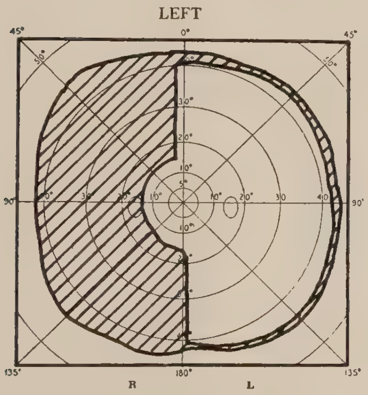
Case B-70. Pituitary blindness.



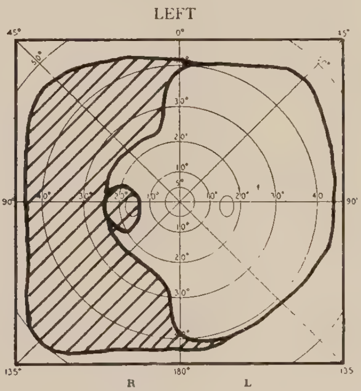
No. 1. July 31, 1923.



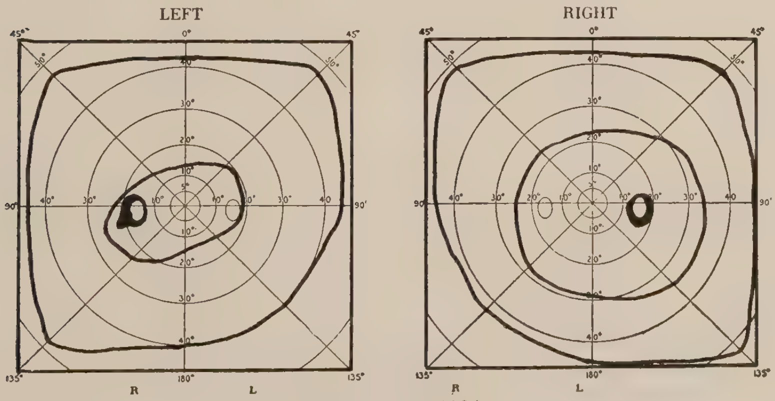
No. 2. Sept. 8, 1923.



No. 3. Dec. 13, 1923.



No. 4. Feb. 20, 1924.



No. 5. May 3, 1924.

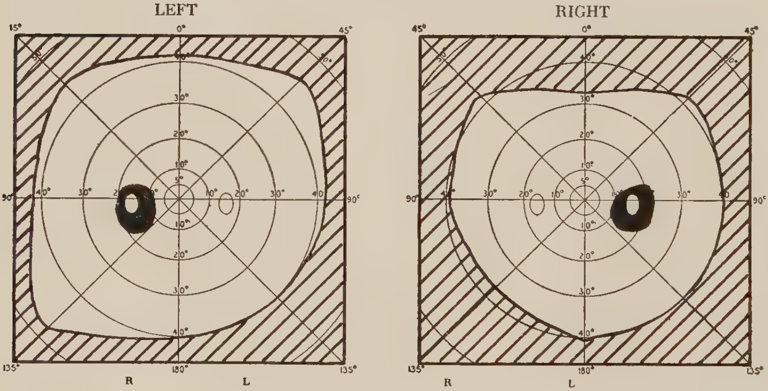
cept for persistence of the yellow discs. Her sugar tolerance had become 50 per cent above the normal, indicating a functional involution of the posterior lobe to a terminal under-active state. The patient also reported a partial resumption of the menstrual function.

CASE B-71. The patient's chief complaint was of a progressive blindness which had been first apprehended some seven months before. A diagnosis of neuro-paralytic keratitis had been made and treatment instituted, but without success.

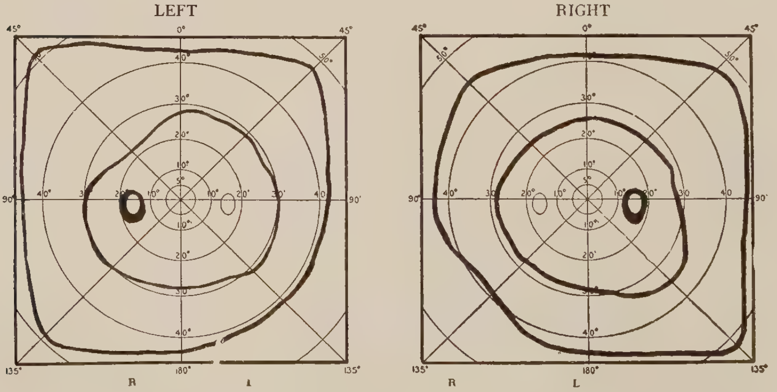
Family History: Four siblings were living and well. The father died of "growth in throat"; the mother, of old age.

PLATE 3

Case B-71. Pituitary blindness.



No. 1. Dec. 5, 1923.



No. 2. April 23, 1924.

Past History: In addition to the usual minor ailments, the patient reports scarlet fever in childhood, an appendectomy at 36, and recently the extraction of a number of teeth. She had been subject to headaches in recent years and some emotional instability. Menstruation began at 13; the periods were regular, every 28 days, with no pain, and normal amount. Her last period was eight months earlier; she is in the menopause.

Physical Examination shows a well developed, short, white woman of 49. She is somewhat obese, with a tendency to girdle distribution. The general physical examination disclosed no other abnormalities.

Laboratory Summary: The patient was 29 per cent over weight, with slightly low basal rate (the value recorded being probably somewhat high). She showed ample protein intake, with a high residual fraction of the urine nitrogen; sugar tolerance depressed; significantly high blood uric acid; a slight relative lymphocytosis and 4 per cent eosinophilia.

X-Ray: Shows some obscuration of the left antrum, increased density of the pituitary and erosion of the posterior clinoid process; also a retained root of the left first upper bicuspid.

Eye Examination showed marked impairment of vision; cornea and vitreous humour in both eyes somewhat hazy; yellow discs; blind spots enlarged; right form field contracted, left slightly so.

Diagnosis: Pituitary dysfunction, anterior lobe under-, posterior lobe over-active.

This case was also one in which operation offered, but doubtful hope of benefit for serious risk. Medication with anterior lobe pituitary substance was instituted with definite improvement in vision, as can be shown by the accompanying figures.

TABLE XIII-a

DISTANT VISION RECORDS

Date	Right	Left
September 9, 1923.........	20/500	20/150
December 5...............	20/1000	20/150
January 2, 1924...........	20/200	20/80
February 27...............	20/150	20/40
April 23..................	20/80	20/40

The fields became practically normal and there was distinct reduction in the size of the blind spots (see plates).

The improvement here noted was probably due, in part at least, to an improvement in metabolism resulting from the glandular correction. In the supervening years there has been some loss of acuity, but the progress has been slow and the present status much superior to that at the initial contact.

DEAFNESS

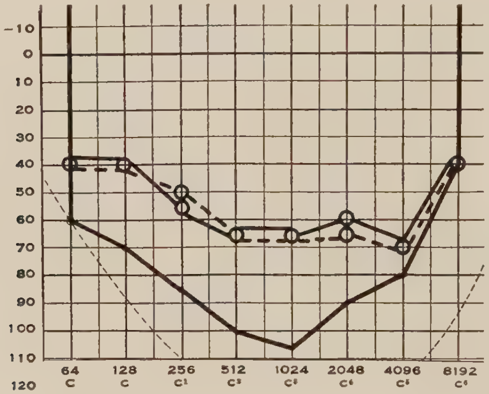
CASE B-238. The patient's complaint is of a bilateral loss of hearing. Eight years ago she had several severe sore-throats, to correct which a tonsillectomy was performed. The deafness, which was remarked just prior to the operation, has been progressive to the present.

Family History was not significant, except for two maternal uncles, who were both deaf following abscessed ears in childhood, and a brother who is also somewhat hard of hearing.

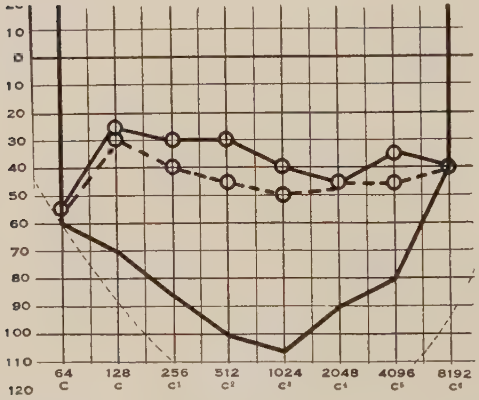
Past History: The patient had the usual children's diseases; an appendectomy one year ago; a laparotomy three years ago for unknown cause. She has had several breast abscesses. She has been married six years, has had no children, but three miscarriages, the most recent being eight months ago and following a long automobile ride, The catamenia began at 16; the periods have been irregular and have not resumed since her last miscarriage. There have been attacks of vertigo during the past six months, but no headaches. She has lost forty pounds in past few years, having dieted rigorously for obesity.

PLATE 4

Case B-238. Pituitary disease with deafness (otosclerosis).



No. 1. Dec. 30, 1924.



No. 2. Aug. 5, 1925.

Physical Examination showed a well developed and nourished white woman of 49. Beyond a partial nasal obstruction and her deafness the examination disclosed no abnormalities.

Laboratory Summary: With a sitting height index of 0.51, the patient is 8 per cent above her predicted weight. This indicates that at the height of her obesity (v. s.) she was nearly 50 per cent overweight. The basal metabolic rate is low; the blood pressure somewhat below normal. The urine shows albumin; its composition indicates a low protein intake; the residual nitrogen is slightly high. Her sugar tolerance is but half the normal. The blood uric acid is high. There is a slight secondary anæmia and the blood is lymphoid in type.

Eye Examination shows yellow discs, enlarged blind spots, some temporal cutting of the right form field, and some contraction of both color fields.

Neurological Examination affords no evidence of organic disease. It defines a social problem which seemingly does not contribute to the present condition.

X-rays of skull, sella, heart and lungs show no abnormalities.

Barany is normal.

Pelvic examination shows normal structures.

Ear examination showed no organic defect.

Audiogram (see plate) demonstrated a marked loss of hearing.

Diagnosis and Outcome: On the basis of the general picture, reenforced by the eye findings, a diagnosis of pituitary dysfunction with the anterior lobe under- and posterior over-active was established, and anterior lobe medication begun. The deafness gradually improved, as is shown in the audiogram (see plate) taken eight months later.

CASE B-130: The patient's chief complaint was of deafness, first noted some eight years ago and progressive since that time, though no great change has been noted in the past two years. Forty years before he had had a discharging ear, which soon cleared up and did not seem to affect the hearing. At the onset of the present condition there had been much tinnitus, but less in the past few years.

Family History showed a distinct tendency to circulatory disease, but otherwise was not remarkable.

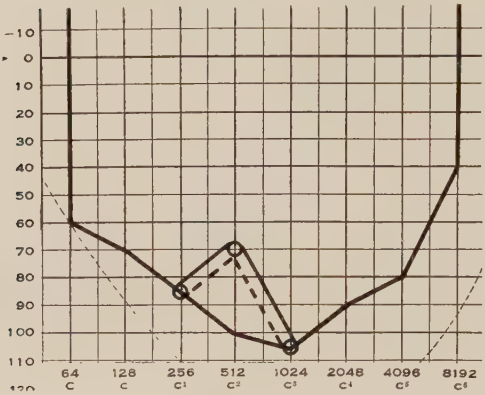
Past History: In addition to the diseases of childhood there is a history of neuritis in the neck; trauma to the head 19 years before with concussion; complete recovery in a week. Gonorrhea was contracted 20 years before, but apparently complete recovery took place. There has been some headache, occasional vertigo, and at one time frequent epistaxis. He has been married nine years; his wife has had several miscarriages and one child which died shortly after birth.

Physical Examination shows a well developed, fairly well nourished white male of 53. with somewhat doubtful teeth. Except for this and a minor cervical and inguinal adenopathy, the physicial examination disclosed no abnormalities. At the time of the examination the patient was unable to receive communication except in writing.

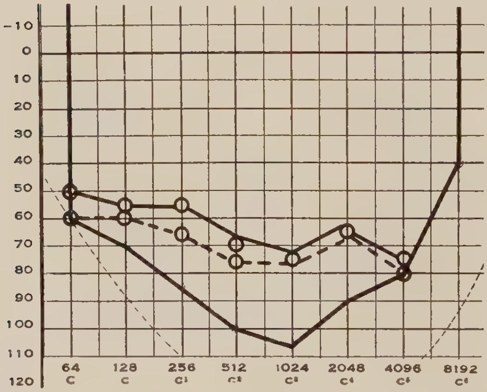
Laboratory Summary: The patient is 10 per cent underweight; the basal rate is low (—24 per cent), as is the pulse rate and the blood pressure. The urine shows casts and sugar. The protein intake is adequate; the partition formula, normal. The "urobilinogen" test is positive. Sugar tolerance is depressed. The nitrogen content of blood including the uric acid is increased. There is relative lymphocytosis. The serological tests were negative.

PLATE 5

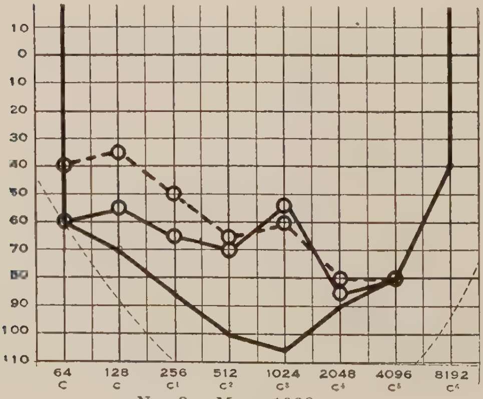
Case B-130. Pituitary disease with deafness.



No. 1. May 19, 1924.



No. 2. Dec. 19, 1924.



No. 3. Mar., 1928.

Ear Examination: The internal ears showed normal function. Some degree of stiffening of the drum heads and ossicles from chronic otitis media was noted.

Neurological Examination gave normal findings.

X-Ray showed sinusitis of frontals, ethmoid and antrum.

Eye Examination showed yellow discs, somewhat enlarged blind spots, and some cutting of the upper fields due to heavy, overhanging eyebrows.

The audiogram showed complete loss of hearing, except at 512 cycles, where there was slight residual acuity (see plates).

Diagnosis: The patient presented a definite sinusitis, gave evidence of lowered kidney permeability, a history in some respects suggestive of a specific eighth nerve involvement, but denied by several negative serological examinations. In addition, there was a suggestion of possible pituitary dysfunction of the common type (anterior lobe under-, posterior, over-active.

Outcome: He was given a therapeutic test with anterior lobe medication. In six months his hearing had improved markedly (see plate); he was able to understand conversation, and this condition has persisted, with possibly slight improvement in the speech area (see plate) up to the present time. Later incomplete examinations have shown a marked improvement in the laboratory picture, including a disappearance of the glycosuria.

ASTHENIA

The next group to be considered is that in which asthenia was the principal difficulty. Cases have been selected illustrating two types, hypo- and dys-functional disorder of the pituitary. The laboratory data are given in the next table, as are those for two cases of headache.

CASE B-28. This patient was studied in the early days of these investigations and the records lack something of the completeness of the later reports. His chief complaint was of a marked fatigability, a slowing down and blunting of the mental processes, and ocular disturbances of a variable and intermittent character (v. i.). He had left college to accept a commission at the time of our entry into the war, served in the A. E. F., and after demobilization had resumed his interrupted studies. When first seen he was experiencing difficulty in completing a very elaborate academic program in which he had been engaged for several years.

Family History: Beyond a younger brother, who presented a retarded mental and physical development, the family history reported no abnormal individuals.

Past History: The patient reported the minor ailments of childhood, but gave a history of general good health and successful athletic activity until he entered the Army. He grew rapidly at or about the time of puberty and attained his height of six feet five inches while still a youth. During his army experience in France he developed a defect of vision, which was later shown to be due to a choroidal hemorrhage, producing a scotoma. After his discharge, as above stated, he resumed his studies and the remaining history was uneventful, except for the gradually progressive loss of physical and mental endurance.

TABLE XIV

		Asthenia		Headache	
		Number B-28	Number B-160	Number B-127	Number B-186
Diagnosis	Anterior Lobe	−	−	−	+
	Posterior Lobe	−	+	+	+
Sex		Male	Male	Male	Female
Age	(yrs.)	27	38	29	31
Height	(cm.)	195	183	163	170
Weight	(kgm.)	86.5	66.0	52.0	65.1
Weight	Dev. (%)	−4	−14	−7	+1
Lung Volume	Dev. (%)	+18	−24	−11	−31
Basal Metabolism	Dev. (%)	−13	−7*	−15	+18†
Pulse	(per min.)	56	72	57	74
Blood Pressure	(mm.)	118/64	120/82	102/64	124/84
Temperature	(deg. F.)	97.1	97.2	97.4	98.6
Alveolar CO_2	(mm.)	55	44	**33**	−
Urine Volume	(c.c.)	2250	1360	1430	2000
Spec. Grav.		1.013	1.017	1.015	1.012
Albumin		0	0	+	+
Casts		0	0	0	0
Sugar		0	0	+	0
Total Nitrogen	(gms.)	13.48	10.92	11.16	13.46
Residual Nitrogen	(%)	2.7	3.5	6.9	5.1
"Urobilinogen"		+	+	0	0
Phen. Sulph. Phth.		90	56	67	36
Galactose Tolerance	Dev. (%)	+67	−67	−67	−50
Non-Protein Nitrogen	(mgm.)	31	42	36	37
Uric Acid	(mgm.)	4.9	4.8	4.2	3.0
Sugar	(mgm.)	88	104	73	86
Haemoglobin	(%)	95	95	95	100
Erythrocytes	(10^6)	5.19	5.17	5.08	5.30
Leucocytes	(10^3)	7.50	5.70	6.90	6.40
Lymphocytes	(%)	31	36	22	36
Eosinophiles	(%)	0	5	4	0

* Not basal. Patient slightly restless.

† Slightly earlier test showed +40%, but patient nervous and test not basal.

Physical Examination: The patient was a symmetrically developed white male athlete, twenty-seven years of age. The face was the so-called pituitary type, the hands and feet large and well formed, the fingers long and tapering (type "en longe"). His general examination gave no abnormal findings, except for the eye condition to be discussed below, and a few minor varicosities in the lower limbs. This latter is a somewhat characteristic pituitary finding.

Laboratory Summary: His weight was but 4 per cent below prediction, his lung capacity 18 per cent above the most exacting (athlete) standard. The basal rate is below normal (the value —13 per cent is probably not exact, —20 per cent, obtained a few days later, being more nearly basal); the pulse is slow. The urine was normal, save for a positive test for "urobilinogen." The sugar tolerance was much above the normal; the blood uric acid high; the blood morphology substantially normal.

X-Rays showed a normal sella and large frontal sinuses.

Barany tests showed intact and normally functioning labyrinths, with nystagmus unusually small in amplitude.

Eye Examination showed yellow discs, enlarged blind spots, and fields which were normal except where influenced by the scotoma. There was an absolute scotoma in the left side of the right field; a large absolute scotoma in the left field. In addition, there were several "moth eaten" areas in both eyes, due to degenerative changes in the retina and underlying choroid.

Diagnosis: The above picture defines a present bilobar hypofunction of the pituitary. The patient's physical habitus makes it seem probable that there was an early hyperactive phase at puberty, at least of the anterior lobe, which had spontaneously arrested.

Outcome: Medication with the components of the whole pituitary gland produced a marked improvement in the clinical picture, and he was able, not only to complete his academic program successfully, but to resume his athletic activities and row on a successful varsity crew. The eye condition has remained unchanged, the initial damage being permanent in its results.

CASE B-160. The patient's *Chief Complaint* was of marked asthenia, accompanied by severe supraorbital headaches. These were frequently associated with nausea and vomiting, relief following the latter. They came originally at monthly intervals, latterly every week or ten days. The whole condition was of some fifteen years' duration.

The *Family History* was not relevant, except for one sister, who died of diabetes.

His own Past History was almost equally negative. He had severe pneumonia at the age of two, and a temporary (?) cardiac disturbance, seemingly following severe influenza at the time of the epidemic. Beyond these, he has had no serious illnesses, but has never been robust. He has been married ten years; his wife has borne two children; she has had no miscarriages.

The *Physical Examination* showed heart and lungs normal; teeth show much dentistry; there is a minor inguinal adenopathy. The patient is six feet tall, a fairly well developed and nourished white male of thirty-eight.

Laboratory Summary: He is somewhat underweight and below his predicted lung volume. The basal rate is below normal (see table foot note); the urine gives a positive "urobilinogen" test; his sugar tolerance is markedly low; the blood uric acid is high, but the non-protein nitrogen is also somewhat above normal. The blood shows a slight relative lymphocytosis and 5 per cent eosinophilia.

X-Ray shows normal skull, sella and heart, some pulmonary fibrosis, and a single infected tooth.

Neurological Examination showed no abnormalities except a slight quantitative difference in the reflexes of the lower extremities.

The *Audiogram* showed slight but definite impairment of hearing (17 per cent).

Eye Examination recorded yellow discs, slight blind spot enlargement, and somewhat contracted fields.

Diagnosis:—The picture as given above defines a pituitary dysfunction with the characteristic formula.

Outcome: On the basis of this diagnosis anterior lobe *medication* was prescribed. The patient reported ten months later that his general level of endurance was practically normal, that he had had five months' freedom from headache, and in the remaining interval an occasional and not severe headache. A brief laboratory examination showed a normal basal rate, blood chemistry and morphology; no change in the audiogram, and practically normal eye findings.

HEADACHE

CASE B-127. The patient originally came to the hospital with what was apparently an attack of renal colic. Physical examination, x-ray and other observations failed to substantiate the diagnosis, and the condition cleared up spontaneously during his hospital residence. He was transferred to us from the Surgical Service, as radiography showed a skull configuration suggesting acromegaly.

The present complaint is of headaches which began three years ago. Originally they were intermittent and relatively infrequent, but for some months past they have increased significantly in frequency and severity. They come over the right eye, but usually involve the whole frontal region, but do not radiate from this area. They are not associated with visual or gastric disturbances.

Family History: The patient was born in Russia and came to this country as a youth. He knows nothing of his family history except that he has five siblings living and well in this country.

Past History: The significant features are an earlier hospital admission for diabetes (undoubtedly a pituitary glycosuria); congenital (?) absence of a sense of smell; marked irregularity of the bowels, the usual interval being three or four days (seemingly a physiological peculiarity); some loss of hair from the vertex, but not from other parts.

Physical Examination: The patient is a well developed, slender white male of twenty-nine. The face and skull are markedly asymmetric with protruding, prognathous lower jaw. Some loss of hair over the ears is noted. The remaining findings are substantially normal.

Laboratory Summary: He is 7 per cent underweight; the basal rate is below normal; the pulse, blood pressure and temperature are moderately reduced; the urine shows sugar and albumin, but is otherwise normal, as is the nitrogen partition; sugar tolerance is much depressed; blood uric acid is high, and a leucoid blood with 4 per cent eosinophilia is present.

Neurological Examination gives substantially normal findings.

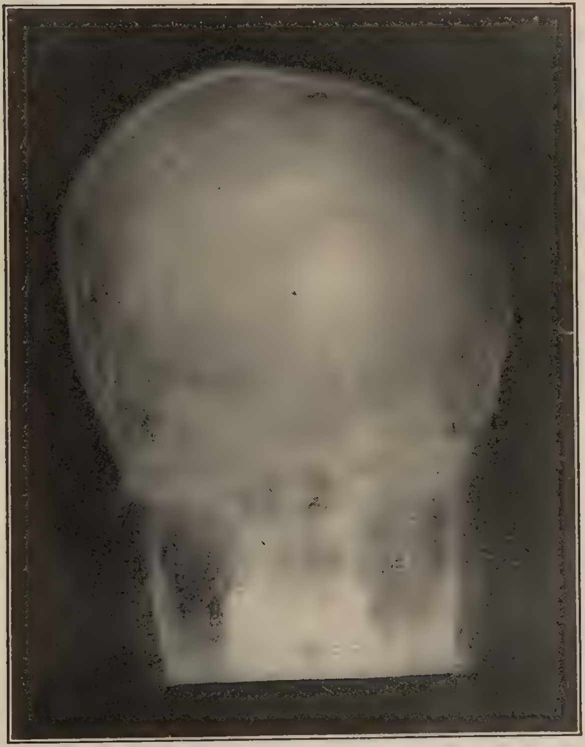
Eye Examination shows yellow discs, enlarged blind spots, and normal fields.

The *Barany* tests are normal.

X-Rays show normal heart, lungs and hands; infected teeth; very irregular and asymmetric skull with long prognathous jaw, prominent diploic veins and large frontal sinuses. The sella is small with heavy anterior and posterior clinoids (see plate).

PLATE 6

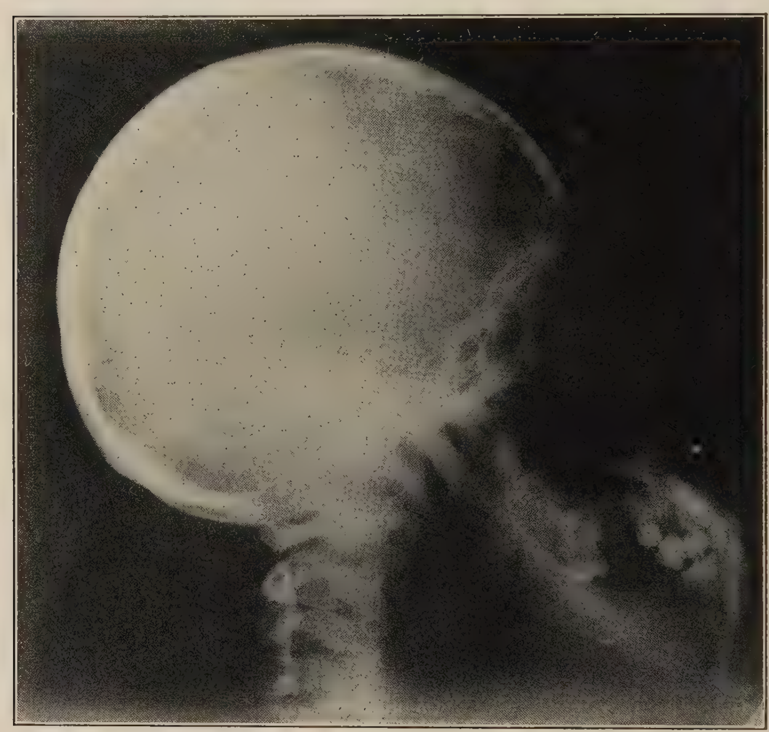
Case B-127. Anterior-posterior x-ray of skull.



The x-ray plates would seem to indicate that the lateral asymmetry of the patient's skull was repeated in the sella with an intrasella space like a truncated cone.

Diagnosis: The patient seems to present a case of aborted acromegaly, with the pituitary, at time of observation, in the characteristic dysfunctional state.

Outcome: The patient was placed on anterior lobe *medication* and for a time showed very definite improvement in his clinical condition. His grade of intelligence was rather low and after a time he failed to follow his medication consistently. He then acquired syphilis and passed under other care.



Case B-127. Lateral x-ray of skull.

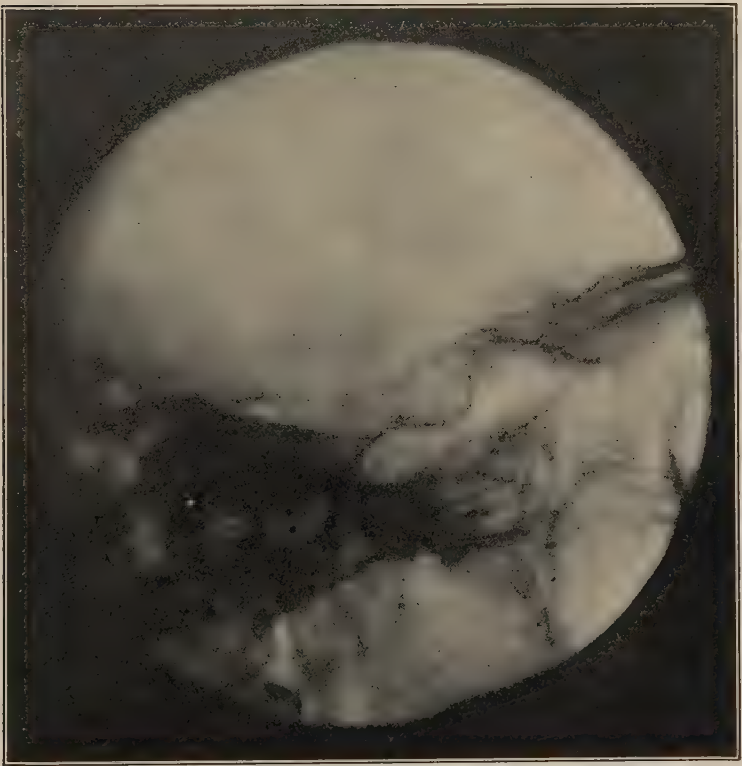
CASE B-186. The patient's chief complaint was given as headache complicated by polyuria and irregular menstruation. The headaches began at puberty, lasted from two to twenty-four hours, and came at irregular but frequent intervals. They were located in temples and vertex. Latterly they have been accompanied by vertigo and faintness. The polyuria began at fifteen and has been progressive except for a brief interval in 1918, following the influenza. The catamenia was established at thirteen, but was very irregular (increased interval) until seventeen, when they assumed a normal rhythm up to a year ago. At this time a tonsillectomy was performed, following which the patient has had but five periods, although the flow has increased somewhat.

Family History: The father is reported as having been an invalid all his life, to have been a sufferer from headache, and "to have suffered from one form of diabetes as a young man." The remaining history is irrelevant.

Past History: Beyond the facts already noted, there was a probable pneumonia; an attack of rheumatism a year ago, for which the tonsil operation was performed; at this time a swelling in the neck in the neighborhood of the thyroid appeared, which "was reduced by x-ray"; some night sweats; otherwise nothing significant.

Physical Examination: The patient was a very well developed, tall, muscular white female of 31, of a distinctly masculine type. The facies is suggestive of the characteristic acromegalic formula. There is marked hypertrichosis with tendency to masculine distribution. There is a slight strabismus in the left eye. The breasts are small. There is slight dullness over the left lung (residual from the earlier pneumonia). Otherwise the findings are normal.

PLATE 6-a



Case B-186. Hyperpituitarism. X-ray of sella.

Laboratory Summary: The basal metabolic rate is slightly above normal, the urine volume at this time ample, but not excessive, and otherwise normal except for albumin. Sugar tolerance was at half the normal level. The blood chemistry and morphology were normal.

The *Eye Examination* shows normal fundi, greatly enlarged blind spots (more in right) and significantly contracted fields.

The *Neurological Examination* gave no evidence of organic nerve disease.

A *Pelvic Examination* gave entirely normal findings.

X-Ray showed normal heart and lungs; the sella shows partial bridging of the posterior clinoids, but the cavity approximates the normal in size.

Diagnosis: On the basis of the above findings a diagnosis of bilobar hyperpituitarism was offered.

Outcome: As the condition did not seem of the utmost severity, operation was postponed and x-ray irradiation instituted.

The results of the first series of treatments can best be tabulated.

TABLE XIV-a

Date	Basal Rate	Wt. (kgm.)	Comment
December 15, 1924......	+23%	66.0	Feels better
January 8, 1925.........	+17%	65.9	Feels better
January 15.............	+17%	65.5	Feels better
January 27.............	+11%	65.6	No more headaches
February 12............	+16%	66.3	No more headaches
February 26............	+ 8%	66.6	No more headaches
July 31.................	— 5%	66.1	No more headaches

After a period of practical freedom from headache there was a resumption, and treatments were again instituted, the basal rate having gone up to +20 per cent. This second series of treatments was effective, but there have been one or two further recurrences, all of which have responded to radiation. No complete studies have been made, but the eye examinations have been repeated at intervals. The latest (February 28, 1928) shows normal fields and blind spots, and the patient reports practical freedom from headache. The menstrual function has improved, though there is still some irregularity. Only the polyuria has failed to show real improvement and the patient still has intervals when she eliminates from 5,000 to 7,000 cc. daily. A possible explanation of this might lie in the persistence of an earlier damage to the mamillary bodies which is uninfluenced by the x-ray therapy.

OBESITY

The next group of patients presents some interesting cases of obesity. The third of the group (B-92) is interesting as a case presenting an inversion of the usual dysfunctional formula. Certain significant data are collected in Table XV.

CASE B-289. The patient's chief complaint was obesity. Was obese as a child, but from the ages of eleven to nineteen had gained two hundred pounds at an apparently uniform rate. This would correspond to a weight of one hundred and thirty pounds at the age of eleven. The appetite is good, but is regarded by the patient as not excessive. He consumes a great deal of candy. He never perspires, except on the feet. He shaves only once a month, but the body hair is normal. He is nervously unstable.

Family History is irrelevant, except for a great uncle said to have been very stout.

Past History: He complains of occasional frontal headache; nothing else of significance.

Physical Examination: The patient is a tall, white male of nineteen, very obese and with marked tendency to girdle distribution. He has a short, thick neck and taper fingers. The genitalia are underdeveloped. The body hair is scanty. The abdomen is very heavy and pendulous. The remaining findings are normal. (See photographs.)

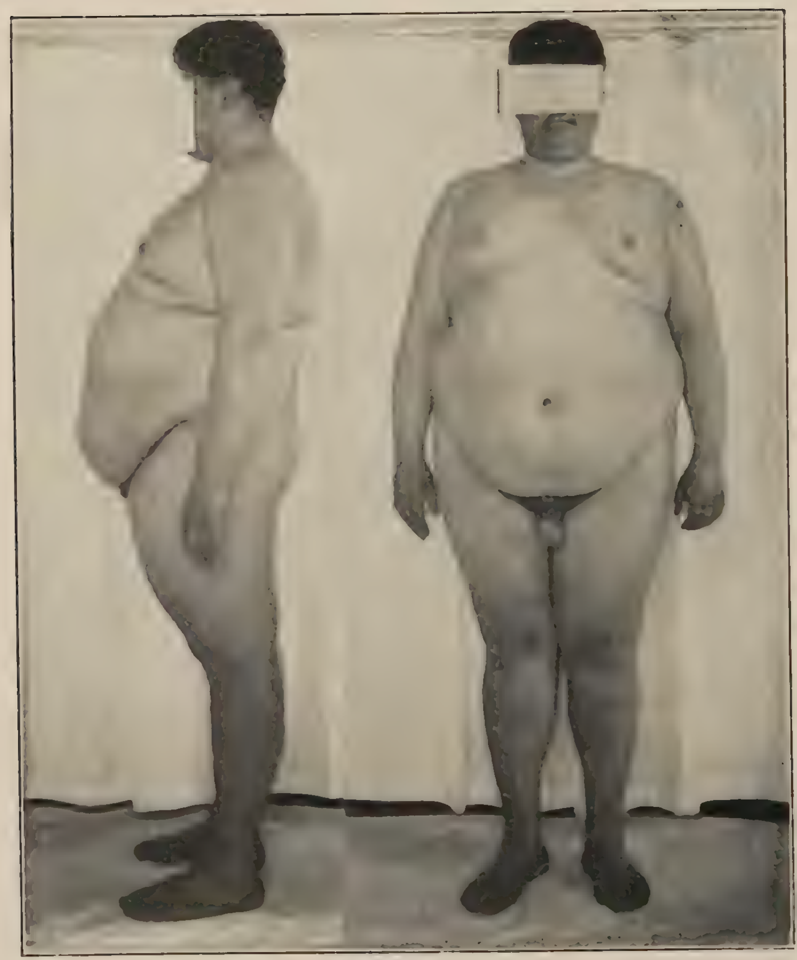
TABLE

		Obesity			
		Nunber B-289	Number C-29	Number B-92	Number B-293
Diagnosis	Anterior	–	–	+	–
	Posterior	–	+	–	+
Sex		Male	Male	Female	Female
Age		19	11	43	27
Height	(cm.)	177	145	156	155
Weight	(kgm.)	150.0	160.5	98.4	114.1
Weight	Dev.	+123	+215	+88	+150
Lung Volume	Dev.	+4	–51	–24	–14
Basal Metabolism	Dev.	–9	–13	+14	–19
Pulse		64	62	87	60
Blood Pressure		124/62	188/80	134/98	118/74
Temperature		97.8	98.6	98.0	98.4
Alveolar CO_2		39	46	40	42
Urine Volume		730	1030	620	910
Spec. Grav.		1.030	1.026	1.018	1.020
Albumin		0	+	0	0
Casts		0	+	0	+
Sugar		0	0	0	+
Total Nitrogen		12.46	11.05	5.78	9.22
Residual Nitrogen		13.9	14.6	17.6	15.0
"Urobilinogen"		0	+	+	0
Phen. Sulph. Phth.		42	46	68	47
Galactose Tolerance	Dev.	+100	–33	+50	–50
Non-Protein Nitrogen		40	30	30	35
Uric Acid		4.9	5.2	4.4	4.3
Sugar		95	81	109	106
Haemoglobin		95	100	100	90
Erythrocytes	(10^6)	4.88	4.80	5.53	6.74
Leucocytes	(10^3)	5.90	8.40	10.70	7.30
Lymphocytes	(%)	42	36	27	34
Eosinophiles	(%)	2	3	2	2

Laboratory Summary: The patient is 123 per cent overweight. His basal metabolic rate is slightly low. The residual nitrogen is high. His sugar tolerance is twice the normal; the blood uric acid is high; the blood is lymphoid in type.

X-Ray shows undeveloped frontal sinuses, shallow sella, normal heart and lungs.

PLATE 7



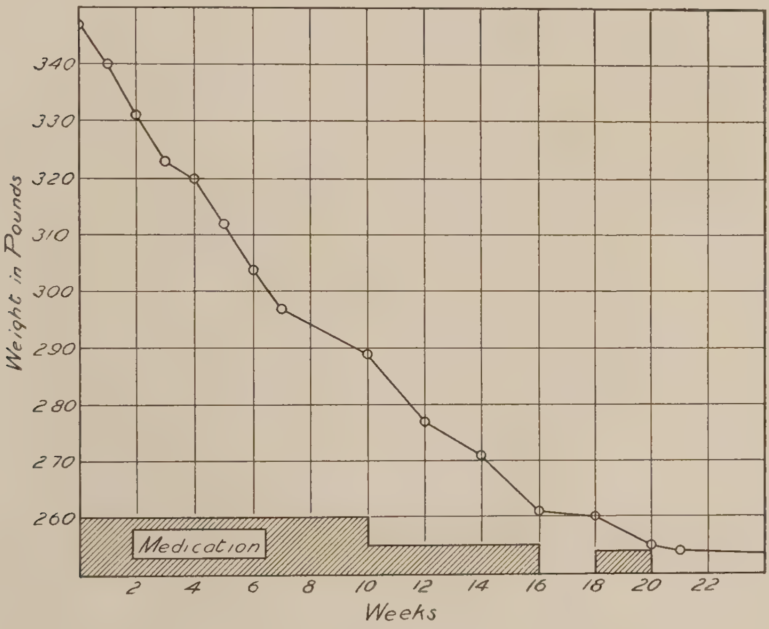
Case B-289.

Neurological Examination shows no abnormalities.

Eyes show yellowish discs, slight blind spot enlargement, and very slight form field contraction.

Diagnosis: The findings indicate a bilobar pituitary failure.

Outcome: The patient was placed on the appropriate *medication* after an interval in which his weight increased to 347 pounds. With some dietary restriction and glandular therapy, the weight loss progressed as shown in the accompanying graph. It will be noted that with suspension of medication the loss of weight stopped. After the twentieth week he discontinued the medication, and at the end of thirty-one weeks (not shown on the chart) he had begun to gain. His weight at this time was 258 pounds.



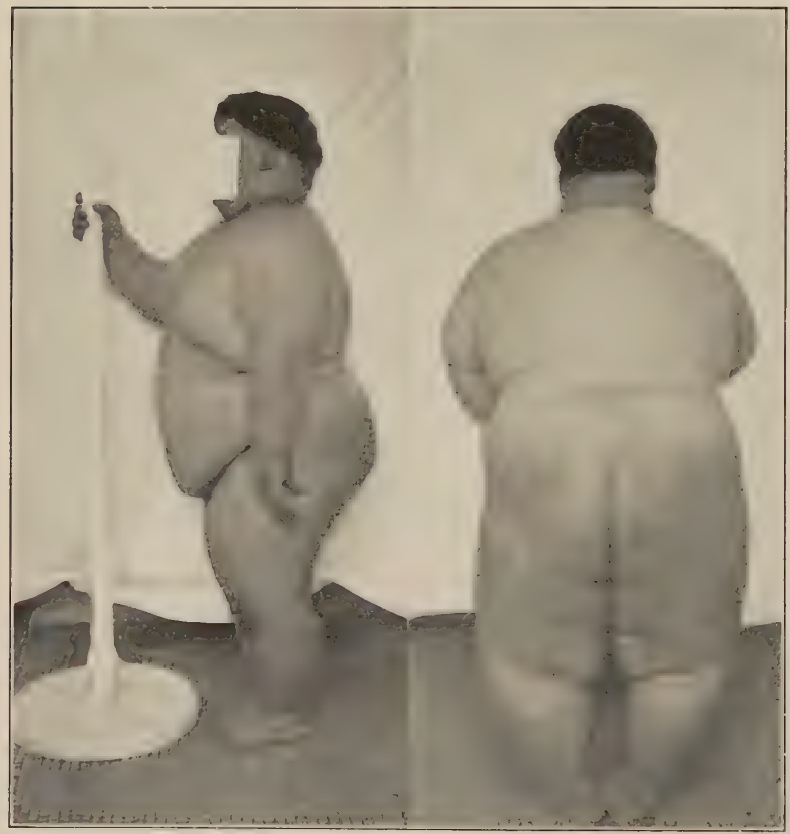
Case B-289. Change of weight with pituitary medication.

CASE C-11, 29, 37, 39. The patient's chief complaint was obesity. At the time of first contact he weighed about 165 kgm. and was 145 cm. tall. He weighed 3.8 kgm. at birth, but began to grow fat at once, so that at six months he weighed 27 kgm. Some time elapsed between his first contact and the first examination; his weight on first admission was 163.5 kgm. A preliminary study was made in February, 1925, which was incomplete (lack of co-operation), but enough data were secured to warrant a tentative diagnosis and medication and diet were suggested. Nine months later an older brother called upon us and gave the information that nothing had been done but dietary restriction at irregular intervals. At his request the patient was re-admitted in November, 1925, and the first complete study (C-29) carried out.

Family History: The mother weighed 200 pounds, but all other members of the family were well built and not obese. The remaining history is not relevant and is not entirely reliable.

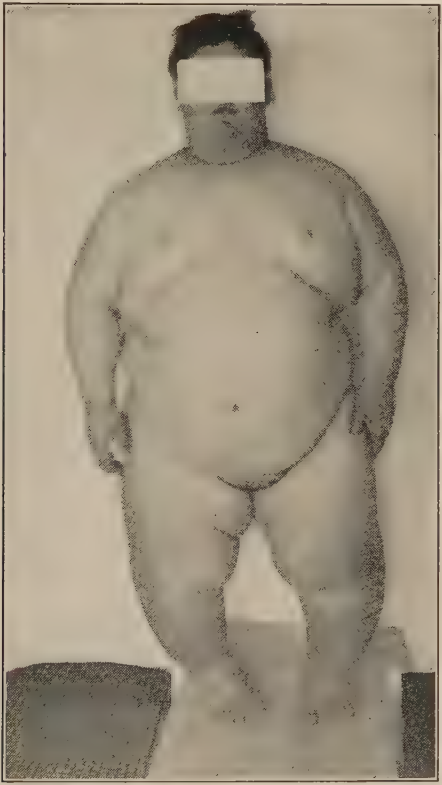
Past History: All of the minor ailments, scarlet fever and diphtheria are reported. He had abscess on the neck requiring drainage. He complained of headaches during which the eyes are "sore." He had marked dyspnoea and palpitation; polyphagia; nocturnal enuresis; occasional incontinence in the daytime. He is easily fatigued and frequently rests by kneeling on one knee. He is of apparent average mentality.

PLATE 8



Case C-29. No. 1. No. 2.

Physical Examination: The patient was an enormously fat Italian boy of eleven. The head was very large and the fat of the scalp could be picked up in folds. Diffuse acniform eruption and many blackheads were present. The breasts were very large. The heart and lungs were hard to define, but apparently normal. The abdomen forms a pendulous apron. But one small testicle is palpable in the large scrotum; there is seen some black pubic hair. He has small hands and feet with tapering fingers. There is maceration on all body surfaces lying in apposition (see photographs).



Case C-29. No. 3.

Laboratory Summary: The boy was 215 per cent above his predicted weight, and as his sitting-height index was 0.561 this was below the truth. The lung capacity was but one-half of prediction. His basal rate was —13 per cent (earlier figures gave a mean of —20 per cent), with high systolic blood pressure. (Independent measurements at this time indicated that the true blood pressure was about 145/80.) The urine showed albumin and casts; the residual nitrogen fraction was definitely high; the "urobilinogen" test was repeatedly positive. The sugar tolerance at this time was somewhat depressed; blood uric acid decidedly high. There was a slight lymphocytosis (?), and 3 per cent eosinophilia.

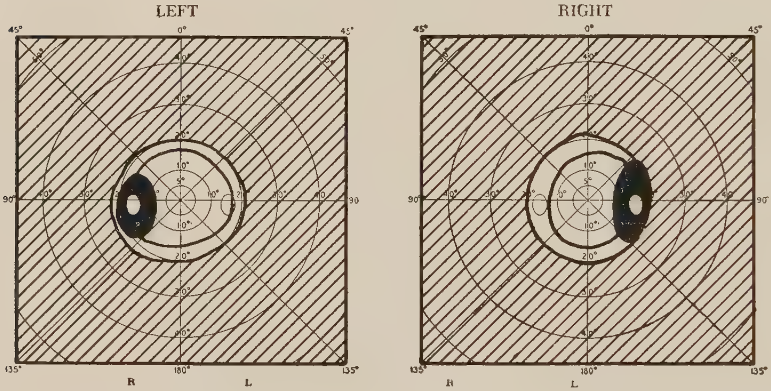
Neurological Examination showed a slowing of the mental processes without arrest of mental development.

Eye Examination showed stiff pupillary reactions, choked discs (4 diopters), very marked contraction of fields (see plate), and greatly enlarged blind spots.

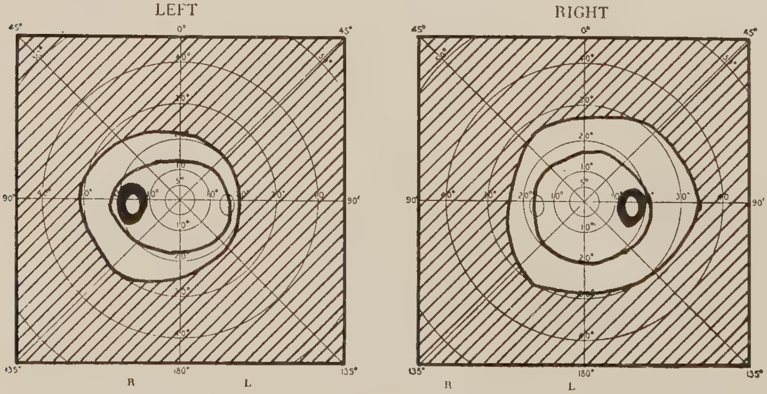
X-Ray showed infected teeth, normal sella (3 sets of plates) and thick skull wall.

A Mosenthal test of kidney function showed normal concentrating power.

An *Audiogram* showed some loss of hearing, most pronounced in the middle range.



No. 1. Nov. 5, 1[illegible].



No. 2. June 25, 1927.

Diagnosis: A diagnosis of pituitary dysfunction with anterior lobe over- and posterior under-active was established.

Outcome: Anterior lobe *medication* with dietary restriction was prescribed. Because of the choked discs, a lumbar puncture was performed, the pressure of the fluid being in excess of 300 mm. The laboratory examination gave normal findings. The patient was placed on Epsom salts and repeated eye examinations were made. Four weeks after the puncture the report was "practically no elevation of discs, cups clearly defined, no hemorrhage, and lymph stasis almost cleared up." During this month the patient lost eighteen pounds. After a further hospital stay, during which time medication and diet were followed, with definite weight reduction (ca. 135 kgm), the patient was discharged. He returned in May (1926) for a check up. The findings showed that neither diet nor medication had been carried out; the weight was 142.3 kgm., the basal rate —22 per cent, and the sugar tolerance unchanged. The other findings reflected the earlier therapeutic measures in more nearly normal levels. The eye findings showed no return of the choked discs; the right blind spot was smaller, the contracted fields unchanged. The parents were urged to continue the medication and diet and the boy sent home. He returned in February, 1927, giving every evidence of complete absence of any care (confirmed later by a member of the family). He had regained all of his lost weight (165.5 kgm.), the basal rate was —23 per cent, the sugar tolerance unchanged (—33 per cent). The left eye had maintained the earlier improvement; the right showed a slight return of the choked disc, but the fields were better and the blind spot smaller (see plate). Recognizing that nothing could be done for him in his home, with the consent of the parents he was placed in a state institution. They were unwilling to let him remain, however, and again took him home. The present status of the case is unknown.

CASE B-92. This case has been selected for the unusual dysfunctional formula presented.

The patient's chief complaints were obesity; unilateral deafness; palpitation and vertigo intensified at the time of her periods. The first condition was of long standing and had been gradual in its progress; the deafness followed childbearing; the other conditions date from a nervous breakdown a year earlier.

Family History: Beyond a familial tendency to tuberculosis, the history is not significant.

Past History: Minor ailments in childhood, mumps without complications in her early thirties, and a susceptibility to infections of the respiratory tract were reported. She stated that she had polydypsia and polyuria, but gave no evidence of these during hospital stay. The catamenia was established at eleven, the periods being regular and normal in amount. She has been married for a number of years and has borne three children without miscarriage.

Physical Examination: The patient was a white woman of forty-three, extremely obese and with a tendency to girdle distribution. The remaining findings were normal.

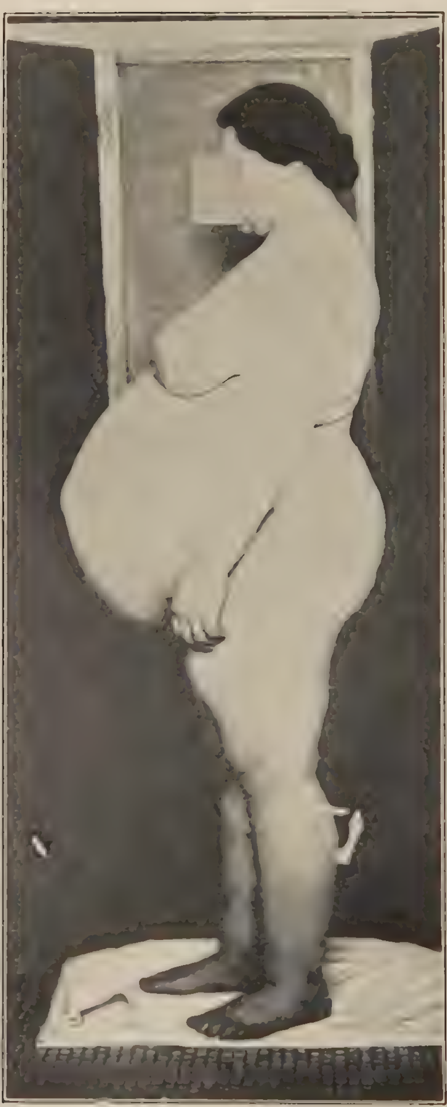
Laboratory Summary: She was 88 per cent overweight; the basal rate was slightly high (several wholly concordant observations); there were somewhat rapid pulse; urine scanty; very high residual nitrogen; positive "urobilinogen"; increased sugar tolerance; high blood uric acid; the blood morphology was normal.

Neurological Examination showed involvement of the vestibular portion of the eighth nerve. Otherwise the findings were normal.

A *Barany* test shows hypersensitivity of the labyrinth.

Ear Examination shows no anatomical changes.

PLATE 9



Case B-92.

X-Ray shows normal skull, sella, and chest.

Eye Examination shows over-filled veins in fundi, slight blind spot enlargement, and normal fields.

Diagnosis: The sugar tolerance is consistent only with a posterior lobe failure or a hypothyroidism of marked degree. This latter is denied by the basal rate. Substantiating observations are the high blood uric acid, the positive "urobilinogen," and the relatively normal levels of many of the other findings. The basal rate is on the upper side of the normal range. Coupled with the somewhat rapid pulse, it is consistent with a very slight overactivity, which is probably merging downward to an ultimate hypofunctional level. A diagnosis of pituitary dysfunction with the anterior lobe over- and posterior under-active was offered, and posterior lobe *medication* recommended.

Outcome: The patient left the state, but a year later opportunity for a partial check up showed a loss of over 20 kgm., a normal basal rate (—2 per cent), and marked clinical improvement.

CASE B-293. This case has been selected because the patient shows the most striking conformity to the conventional formula of fat distribution of the entire series (see photographs). Her chief complaint was of obesity, in addition to which she had a history of convulsions and complained of pain in the lower spine. During the first six years of her marriage she was infertile, and at the end of this period she weighed 64 kgm. In the past five years she has borne four children and had two miscarriages, with a steady increase in weight to her present level of 114 kgm. She has had two operations for the removal of abdominal fat. She stated that for the past year she has had sharp pain and tenderness in the lower spine. The convulsions started three weeks earlier. There is a preliminary sense of pressure over the left chest, and headache, followed by a gradual loss of consciousness; there ensues a tonic spasm of the body lasting no more than a minute or two and accompanied by grinding of the teeth. Several of these spasms occur during the period of unconsciousness and the attack terminates with gradual relaxation. Morphia is the only drug that has proven effective, and the patient was under a heavy morphine dosage at the time of her entrance. Seizures observed during her stay in the hospital did not conform entirely to this formula; there was prompt and complete recovery and the substitution of occult non-narcotic therapy yielded excellent results.

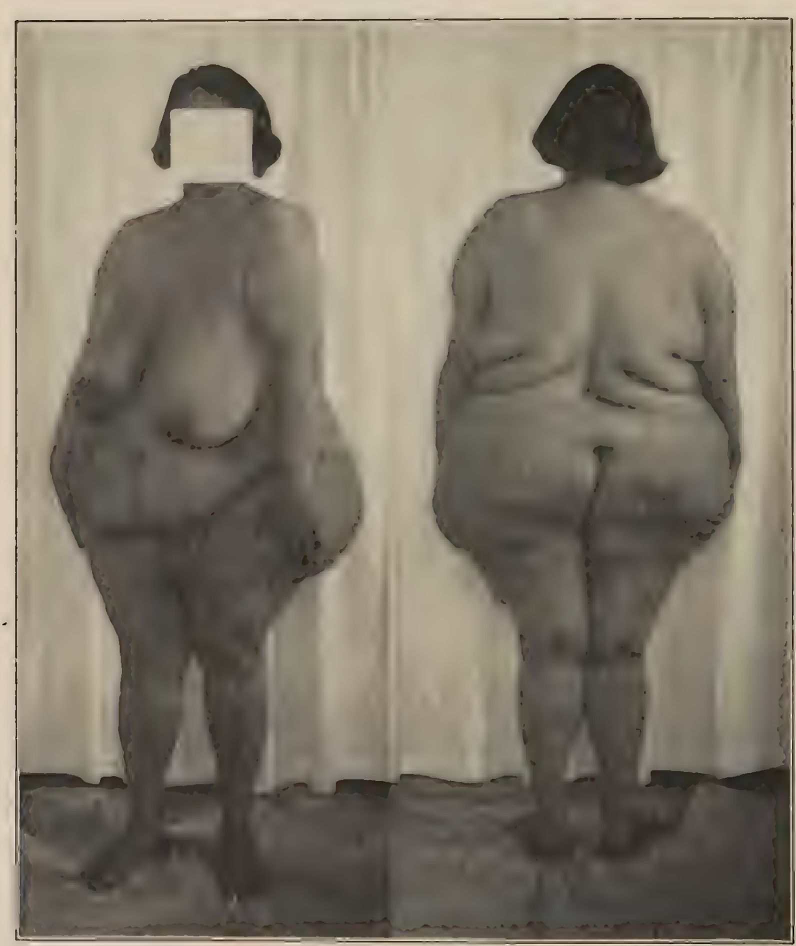
Family History is entirely irrelevant.

Past History: Beyond minor ailments and the facts stated above, the patient had four gall stone operations, the last being removal of the gall bladder. The catamenia was established at eleven and the periods were entirely normal up to the time of her five-year amenorrhea determined by her repeated pregnancies. It is interesting to note that she always conceived before the re-establishment of her periods following childbirth.

Physical Examination: The patient was a white woman of 27, with delicately moulded features, hands, feet, forearms, and lower legs, but with an enormous fat deposit in the middle third of the body. The breasts were very large and pendulous. There was a marked post-operative hernia. The remaining examination, including the spine, gave entirely normal findings.

Laboratory Summary: The patient was 150 per cent overweight, with basal rate below normal. The urine showed casts, sugar, and a high residual nitrogen fraction. The galactose tolerance was reduced to half the normal level; the blood uric acid was high; there was a slight relative lymphocytosis. A few of the patient's measurements are striking.

Plate 10



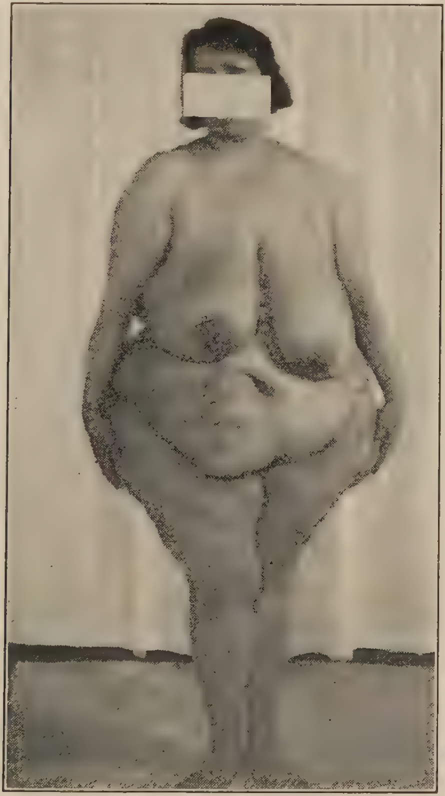
[illegible] No. 1 No. 2

X-Ray showed normal skull and sella.

Neurological Examination offered no evidence of organic nervous disease. The seizures were believed to be hysterical in character or possibly of toxic origin deriving from an endocrine condition.

TABLE XV-a

Chest	109 cm.	
Waist	110 cm.	
Hips	160.5 cm.	
Upper arm	Right 40	Left 42
Forearm	Right 25	Left 25
Wrist	Right 15	Left 15
Thigh	Right 81	Left 79
Calf	Right 41	Left 39
Ankle	Right 21.5	Left 20.5



Case B-293. No. 3.

Eye Examination showed yellow discs and so great a symmetrical contraction of the fields (10 degrees) that the blind spots could not be delineated.

Diagnosis: The picture given above defines a pituitary dysfunction of the usual type. Anterior lobe medication was advised, but the patient passed out of our knowledge after showing some improvement.

An interesting feature is the patient's fecundity after a six-year sterile period.

STERILITY

An interesting group of cases are those exhibiting sterility, apparently the result of pituitary malfunction, as they become fecund with the correction of the endocrine impediment. This whole question is now under extensive investigation and will be reported in detail at a later date. A single typical case is reported in the next table (Table XVI). In this table are given two series of observations on the same patient which illustrate the tendency to functional involution which this glandular structure frequently undergoes. Although a diagnosis was estab-

TABLE XVI

	Sterility	Progressive Change		Growth Arrest	
	Case No. S-260	Case No. B-162	Case No. B-162-a	Case No. B-190#	Case No. S-1605†
Diagnosis............Anterior...	–	–	–	–	–
Posterior...	?	+	–	N	+
Sex..........................	Female	Female	Female	Male	Male
Age.................(yrs.)......	34	36	38	16	19
Height..............(cm.)......	181	160	160	132.5	150.6
Weight..............(kgm.).....	88.3	76.8	80.7	22.0	35.0
Weight Deviation.....(%).......	+20	+22	+28	–34	–25
Lung Volume Dev....(%).......	–24	–24	–	–16	–24
Basal Rate Dev.......(%).......	+2*	–12*	–8*	–17	–20
Blood Pressure.......(mm.).....	134/92	112/68	106/58	90/52	96/40
Pulse...............(per min.)..	62	68	57	68	60
Temperature.........(deg. F.)...	97.4	97.5	97.9	98.1	97.8
Alveolar CO_2.........(mm.).....	35	–	–	40	40
Urine Volume........(cc.).......	1640	2440	1450	370	410
Specific Gravity................	1.016	1.009	1.015	1.023	1.028
Albumin........................	0	+	0	0	+
Casts..........................	0	+	0	0	0
Sugar..........................	0	0	0	0	0
Total Nitrogen.......(gms.).....	12.47	8.97	8.96	4.78	5.28
Residual Nitrogen....(%).......	3.8	10.1	9.3	21.8	11.0
"Urobilinogen".................	+	+	0	0	0
Phen. Sulph. Phthal...(%).......	55	32	75	30	58
Galac. Tol. Dev......(%).......	–	–75	>+50	±0	–33
Non-Protein Nitrogen.(mgm.)....	24	39	–	29	32
Uric Acid...........(mgm.)....	5.0	2.4	3.6	2.2	2.7
Sugar...............(mgm.)....	130*	94	98	89	91
Haemoglobin.........(%).......	95	90	90	90	85
Erythrocytes.........(10^6)......	4.76	5.31	4.91	4.66	5.00
Leucocytes...........(10^3)......	7.90	9.25	6.15	5.45	8.15
Neutrophiles.........(%).......	33	53	70	38	56
Lymphocytes.........(%).......	57	44	24	55	39
Eosinophiles.........(%).......	0	0	2	3	1
Monocytes...........(%).......	10	3	4	4	4

* Too high. Patient nervous.
† September, 1924.
‡ September, 1927.

lished during the first contact, the patient declined to undergo medication and the later series of tests were uninfluenced by any intermediate therapy.

CASE S-260. The patient's chief complaint was sterility, her six years of married life with constant exposure having failed to produce pregnancy. Her husband has been shown to be fertile.

Family History was irrelevant.

Past History: The patient records minor ailments, a period of rapid growth from eleven to fourteen, at which age she established the catamenia. This latter is not remarkable except for scanty periods and headache. She was married at twenty-eight and shortly thereafter gained thirty pounds in weight. She has been fatigable; has never had much perspiration, although she feels the heat markedly. Two years ago she was given ovarian extract which produced benefit in her general condition, but had to be discontinued, as it produced palpitation.

Physical Examination: The patient was a very tall white woman of thirty-four, with a definite "girdle" obesity. The remaining findings were normal.

Laboratory Summary: The report is incomplete, since full cooperation could not be secured. She was 20 per cent overweight. The basal rate was not satisfactorily determined, but undoubtedly below the normal level. The urine was practically normal, except for a positive "urobilinogen." She had high blood uric acid and markedly lymphoid blood. The sugar tolerance could not be determined.

X-Ray showed bony bridging of the sella.

Eye Examination showed yellow discs, slightly enlarged blind spots, and a contraction of the red fields.

Diagnosis: Recognizing the numerous omissions from the diagnostic picture, a tentative diagnosis of pituitary disease was based on the available information. The anterior lobe was construed to be underactive; the posterior was undetermined.

Outcome: The patient was placed on anterior lobe *medication* and inside of three months became pregnant, ultimately delivering a normal child.

CASE B-162, 162-a. This case is presented as showing the natural course of a pituitary disorder uncomplicated by glandular therapy. The patient was first seen in May, 1924.

Her chief complaints were of some frontal headache, fatigue and gastro-intestinal disturbance. She dates the onset from an operation for the removal of a tube and ovary, the other uterine adnexa having been removed eighteen years previously. As a matter of fact, while a laparotomy was performed, the ovary was not removed and the patient has continued to menstruate up to the present, a fact that seemingly has not appeared to her to be inconsistent with her supposed condition. The headaches originated in the frontal region and radiated backward. They were chiefly associated with her periods. The fatigue was continuous and unrelieved by eighteen hours' continuous sleep in which she frequently indulged. She had frequent attacks of excessive perspiration; there were frequent attacks of nausea and vomiting, which began after her first pelvic operation (18 years ago). In the last three years there have been intermittent attacks of diarrhoea. In addition, there were numerous minor complaints.

Family History: Completely irrelevant.

Past History: The patient had scarlet fever and several minor ailments in childhood. Nine years ago she was in bed for sixteen weeks with an attack which began with headache, vomiting, and fever, caused complete paralysis of the lower limbs and from which she recovered completely. She weighed 53 kgm. at thirty-two, and at the time of this study, four years later, 76.8 kgm. In addition to those given above, she had some operation on the bladder fourteen years ago. She had chronic cough from the age of nine. She matured at twelve years, the first period following a dilation. Menstruation was irregular with shortened interval to eighteen; since then it has been regular at twenty-day intervals with five-day periods. She has been married eighteen years with three pregnancies, resulting in one premature birth, one miscarriage, and one full term, normal child.

Physical Examination: The patient was a well developed white female of thirty-six, obese and with marked tendency to girdle distribution. The teeth were very poor; lungs normal. Some varicosities were noted in the lower limbs. Neurological and other findings were normal.

Laboratory Summary: The patient was 24 per cent overweight. On account of nervousness, a satisfactory basal rate determination could not be secured; the observed value was below the normal level. There were moderate reductions in the physical measurements; high urine volume; albumin and casts present; high residual nitrogen; positive "urobilinogen"; galactose tolerance greatly reduced; phthalein test low. The blood morphology showed lymphocytosis and 3 per cent eosinophilia.

X-Ray showed normal skull and sella and obscured frontal sinus. There was evidence of healed and calcified lymph nodes at the left apex and a calcified gland in left hilus.

Pelvic Examination showed an intraligamentous cyst in the right vault, but otherwise no abnormalities.

Eye Examination showed marked symmetical contraction of fields and enlarged blind spots.

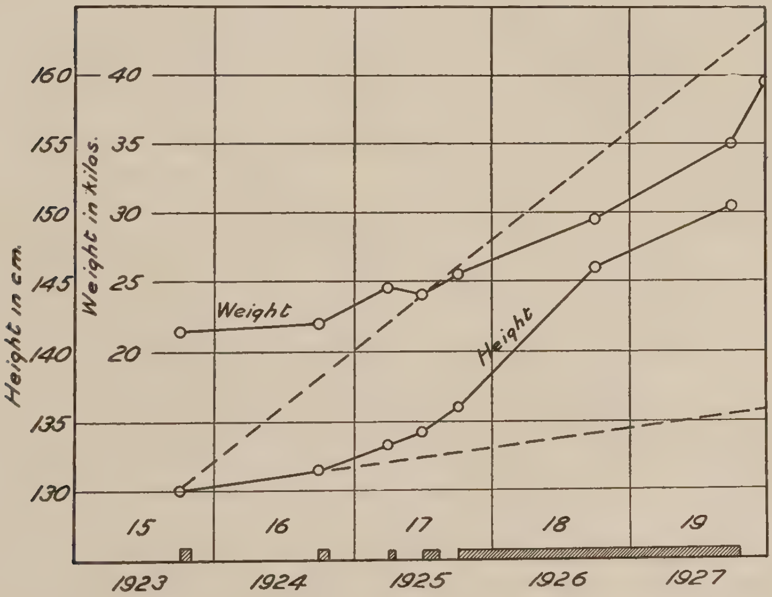
Diagnosis: This general picture was felt to define a pituitary dysfunction of characteristic formula.

Outcome: Anterior lobe *medication* was advised. The patient declined treatment, however, but returned in January, 1926. A partial study was carried out. She had gained some 4 kgm. in weight; again a satisfactory basal rate determination could not be secured, but the observed value left no doubt as to the hypofunctional level of the anterior lobe. The complementary physical findings were slightly lower (temperature excepted); the earlier kidney condition had apparently cleared up entirely, her sugar tolerance had increased to a level over 50 per cent above the normal (she would not complete this test), the blood uric acid was relatively higher, but still normal; the blood had become leucoid in type, with a 4 per cent eosinophilia. The eyes showed further contraction of the fields and enlargement of the blind spots. X-ray findings were unchanged. The general condition was unchanged.

Obviously, the posterior lobe had undergone functional involution during the interim, and the patient had become a bilobar failure. Appropriate medication was recommended, but contact was lost before the outcome could be ascertained.

CASE B-72, 190, C-12, Sp. 25-a-b-c, S-1605. This patient was first seen in September, 1923. A partial study was made, a tentative diagnosis of pituitary dysfunction established, and a brief course of anterior lobe medication instituted. The boy grew an inch during his hospital stay and was sent home to continue his therapy. He returned a year later. It was found that he had made no progress, and enquiry developed the fact that he had had no medicine. A complete study was made (see B-190 in Table XV) and the original diagnosis confirmed.

PLATE 11



Case B-190. Change of weight and height under influence of pituitary medication.

His chief complaint was of inability to swallow. This kept him undernourished. He was also much below the normal height for his years. He had been in good health and large for his age up to 7½ years. He then developed whooping cough and it was stated that the medicine used at this time provoked attacks of vomiting, which continued for one year. Following this, radioscopy disclosed an œsophageal stricture, and three years ago he was dilated, with temporary relief. His difficulty in swallowing is intermittent; at times solids can be taken and at others, even liquids cannot be swallowed. From the time of the whooping cough he grew very slowly, so that he was much undersize for his age. He was referred to us for his dwarfism and for an apparently persistent thymus, disclosed by the x-ray.

Family History was irrelevant.

Past History: Beyond the facts recorded above, there is little of importance.

Physical Examination: The patient was a white boy of sixteen, greatly undernourished and looking like a child of eight. His mental age corresponded to his actual years. The head was disproportionately large. The testes were descended but very small. The genitalia were infantile in type. Beyond a minor cervical adenopathy nothing of importance was observed.

Laboratory Summary: The patient was 34 per cent underweight, with normal sitting height index. The basal rate was 17 per cent below prediction; blood pressure low; respiration somewhat slow. The urine showed poor elimination, but this was undoubtedly due to his low intake. Protein intake was inadequate and the residual nitrogen fraction was very high. The phthalein test was distinctly low. The sugar tolerance at this time was normal; the blood chemistry normal; the blood morphology showed a marked lymphocytosis and 3 per cent eosinophilia.

X-Ray examination showed a substernal shadow to the right of the spinal border; undeveloped carpal scaphoid; an unformed trochlear process of the lower end of the humerus; unformed olecranon; normal skull and sella; cardiospasm—obstruction to barium meal at cardia.

Eye Examinations showed stiff pupillary reflexes, the other findings being substantially normal.

Diagnosis: The genital arrest, the retarded ossification, the dwarfism, and the persistent thymus, all pointed to a developmental arrest. His symmetry and good proportion coupled with the laboratory findings pointed to a pituitary dysfunction in which the anterior lobe was underactive and the posterior, normal, at the time of observation. As there exists no satisfactory evidence of the endocrine property of the thymus—and much to deny it—it was felt that the persistence of this gland was but one more evidence of an arrest in normal developmental changes.

Outcome: Anterior lobe *medication* was again applied for a brief space and the patient discharged with the recommendation to continue it. This was not done, however, and during the succeeding year we had several contacts with the patient at each of which some anterior lobe was given to which he responded (See Graph). At the last of these, finding that his medication ceased when he left the Hospital, we arranged for a regular supply to be sent to him. During the first two years he had gained 6 cm. on an occasional brief period of pituitary (anterior lobe) medication; during the next two with more consistent therapy and in spite of presumptively lowered growth capacity, he has increased 14.6 cm. In the accompanying graph are shown the weight and growth curves over the interval. The dotted lines represent extrapolations, and naturally are devoid of real significance, but are possibly suggestive. The lower shows the predicted height at present had the growth rate of the first year persisted; the upper, the prediction had the boy enjoyed the benefit of adequate medication from the beginning.

During 1925 the boy developed a slight general adenopathy. A biopsy was performed but the tissue removed gave no clear-cut evidence of the presence of Hodgkin's disease. The latter history would render this condition highly improbable.

Nose and Throat findings were normal.

An *Audiogram* showed a slight loss of acuity in the speech area.

He has had a complete laboratory check up at yearly intervals, the data from the latest being given in Table XVI. It will be noted that his basal rate is still below prediction, and this is due to the impossibility of grading the dosage to his needs under the conditions imposed upon us. The throat condition has cleared in large measure, but is not entirely corrected. This has determined the low nutritional intake which has undoubtedly influenced his growth curve on the one hand and his urine elimination picture on the other. The residual nitrogen fraction is approaching normal limits. The phthalein output is now normal, and indication of a better general metabolic level. The sugar indicates a present slight overactivity of the posterior lobe. This has fluctuated during the period of observation, at times being over-, at times under-active. At no time has there been an over supply of the active agents of the anterior lobe, though the degree of hypofunction has fluctuated with the medication and the patient's needs. The lymphocytosis, while still in evidence, is significantly decreased.

X-rays show a mediastinal shadow below and behind the sternal notch; the heart gives some evidence of dilation.

An *Eye Examination* gives normal findings except for yellow discs, the pupillary reflexes being entirely normal. "Urobilinogen" was noted at times in the urine but has apparently disappeared. The earlier adenopathy has largely cleared up. Clinically, the boy is greatly improved, is now in college, and doing very well.

Comment: In reviewing this case one cannot but regret that sustained controlled therapy could not have been followed from the beginning. It is idle to speculate as to results, but with those obtained by highly irregular treatment it may be assumed that the salvage would have been even greater.

EVOLVING ACROMEGALY

CASE S-326, 326-a, B-269, 269-a, 475, 475-a, 475-b, 475-c: This case has been under almost constant supervision since 1924. While it will be reported at length elsewhere in the near future and certain phases of the carbohydrate metabolism have recently been completed by one of our colleagues [Ulrich (54)] it presents certain points of such marked interest as to warrant brief presentation here. The patient is still under observation.

The patient was first seen in July, 1924; he was a powerfully built young man of twenty-four with the typical facies of acromegaly. The chief complaint was of recurrent paroxysmal headache which began in 1921 with increasing frequency and intensity during the interim.

Family History is entirely irrelevant.

Past History: Beyond a few minor ailments and a recent tonsil and adenoid operation, the history was entirely uneventful. A photograph taken in 1916 gives no evidence of acromegaly, but one at twenty, a year before the onset of symptoms, shows well marked and typical changes.

Physical Examination: The patient was a powerfully developed, well nourished white male of twenty-four. The hands were large, the feet of normal size. There was marked generally distributed pilosity. The reflexes were present but somewhat sluggish. The remaining findings were completely normal.

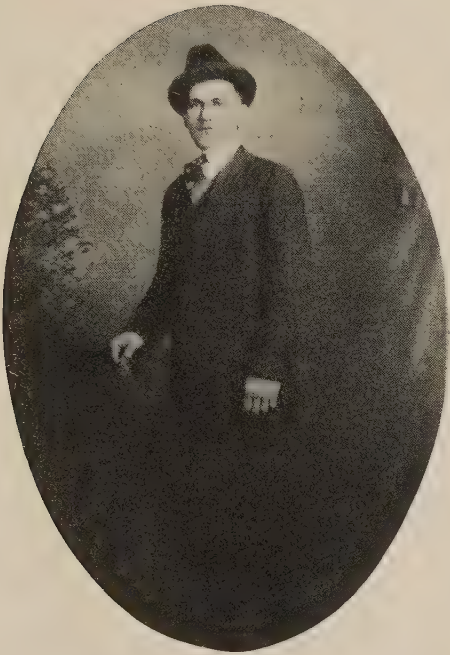
TABLE XVII

	July, '24	Dec., '24	Feb., '25	July, '25	Mar., '26	Dec., '26	Sept. ,'27
	Case No. S-326	Case No. -326-a	Case No. B-269-a	Case No. B-475	Case No. B-475-a	Case No. B-475-b	Case No. B-475-c
Diagnosis.....Anterior...	−	+	+	−	N	+	+
Posterior...	−	+	+	+	+	+	+
Sex....................	M	M	M	M	M	M	M
Age...............(yrs.)	24	25	25	25	26	27	28
Height.............(cm.)	172	172	172	172	172	172	172
Weight...........(kgm.)	83.4	81.2	82.5	87.5	80.5	77.0	69.2
Weight Deviation....(%)	+21	+19	+20	+28	+18	+8	−3
Lung Vol. Dev.......(%)	+9	+1	−2	−3	−24	−2	−21
Basal Rate Dev......(%)	−11	+65	+12	−7	+4	+28	+54
Blood Pressure.....(mm.)	110/55	148/72	130/58	106/60	100/80	106/58	120/78
Pulse..........(per min.)	53	91	68	62	69	76	78
Temperature....(deg. F.)	97.9	97.8	98.0	97.6	98.0	97.8	98.0
Alveolar CO_2.......(mm.)	−	43	41	45	42	48	44
Urine Volume.......(cc.)	1010	7920	1950	1740	2140	1890	1540
Specific Gravity.........	1.017	1.034	1.018	1.014	1.027	1.037	1.038
Albumin...............	0	0	0	+	+	0	0
Casts..	0	0	0	0	0	0	0
Sugar..............(gm.)	0	238	0	0	133	74	78
Total Nitrogen.....(gms.)	7.66	23.92	13.94	11.44	12.75	14.55	4.28
Residual Nitrogen....(%)	5.2	4.8	5.5	9.5	13.9	11.9	3.8
"Urobilinogen"..........	0	0	+	0	0	0	0
Phen. Sulph. Phthal..(%)	46	68	46	46	43	48	44
Galac. Tol. Dev.....(%)	+33	−	−33	−67	−67	−83	−67
Non-Pro. Nitrogen(mgm.)	35	59	27	32	27	26	33
Uric Acid.........(mgm.)	5.1	6.6	3.7	4.3	3.0	4.7	2.4
Sugar............(mgm.)	102	404	99	103	364	334	510
Haemoglobin.........(%)	100	85	80	100	100	90	98
Erythrocytes........(10^6)	5.70	5.42	4.36	5.69	6.07	5.18	5.26
Leucocytes..........(10^3)	9.75	10.40	8.25	11.36	11.50	11.30	21.60
Neutrophiles.........(%)	47	54	46	57	52	53	67
Lymphocytes........(%)	44	39	48	38	40	38	30
Eosinophiles.........(%)	5	6	3	2	5	2	1
Monocytes..........(%)	4	1	3	3	3	7	2

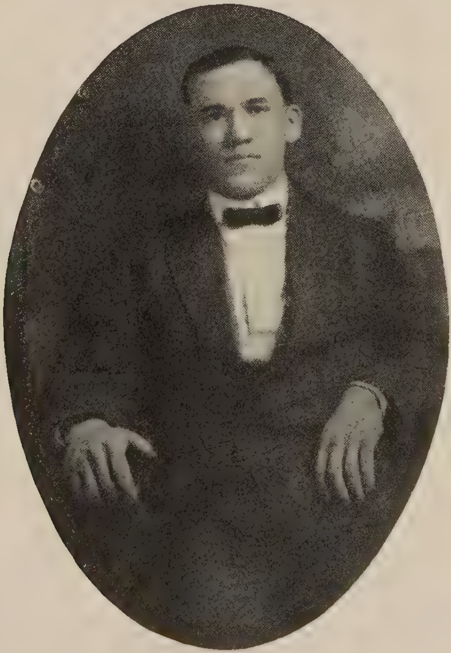
Laboratory Summary: The patient was 21 per cent overweight, with basal rate of —11 percent, blood pressure slightly low and pulse slow. The urine presented a normal picture throughout. The galactose tolerance was slightly high; the blood uric acid definitely above normal; the blood was lymphoid with a 4 percent eosinophilia.

X-Ray showed an enlarged sella with shallow, eroded floor (see plate) and large frontal sinuses.

PLATE 12



Case S-326. Before onset.

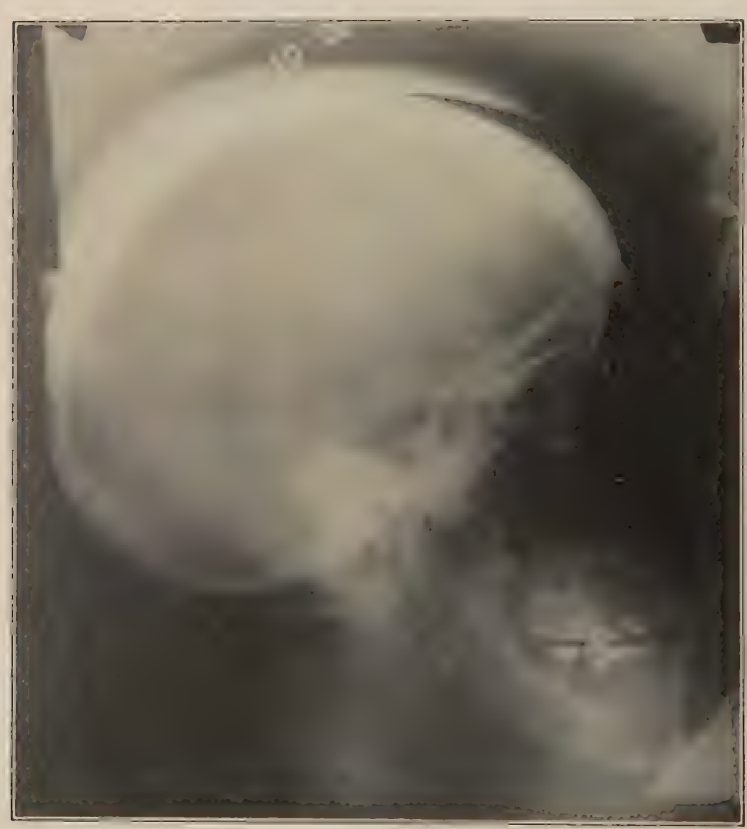


Case S-326. After onset.

The *Barany test* was normal.

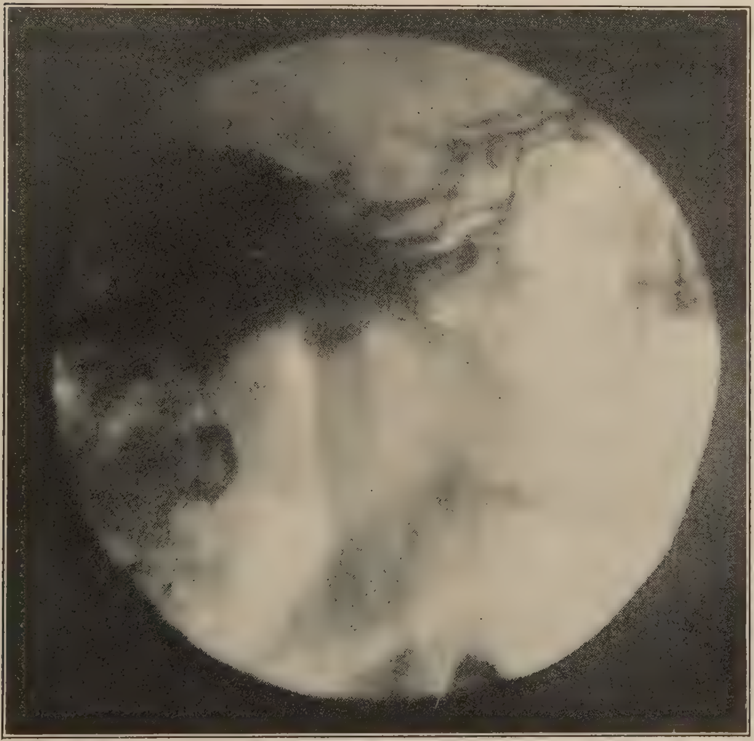
Eye Examination showed 20/60 vision in both eyes, yellow discs with indistinct margins, enlarged blind spots, normal form but contracted (left) color fields.

Diagnosis: From the picture presented the diagnosis was established as acromegaly with the gland in the final or hypo-functional state.



Case S-326. Before operation.

Outcome: As the patient was unable to work, he was retained at the hospital under observation. The condition seemed static, but in September there was a resumption of the headaches, which were very severe. After consultation it was decided to try the effect of deep x-ray irradiation, and on September 29 and October 7 treatments were given. These were followed by complete freedom from pain subsequent to the latter date. The color field showed marked improvement. Treatments were given on October 17 and 25 and November 7, there having been but one slight headache in the interval. The patient desired to go home for Thanksgiving and was given a two-weeks' leave of absence. On his return in mid-December a laboratory check was started with the result that the first day's urine was found to be nearly eight liters and to contain 238 grams of sugar (see 326-a in Table XVII.) He was placed under active anti-diabetic treatment, the details of which are recorded elsewhere (54), and after showing a steadily rising blood sugar with massive insulin dosage, he rapidly returned to normal with full diet, no insulin, and disappearance of the glycosuria, hyperglycaemia, and polyuria. His laboratory picture in February, 1925, showed a mild bilobar overactivity, there being seemingly a recurrence of the earlier state. In June the headaches resumed; in July the anterior lobe had again become hypoactive, but the posterior overactivity had increased (see B-475). X-ray treatments were resumed, but the headaches increased and in October the visual disturbances reappeared. By mid-November, however, the x-ray had again apparently controlled the situation. In a few weeks this was found not to be the case, and Dr. W. J. Mixter was called in consultation. He advised operation, and through his courtesy the patient was transferred to his service at the Massachusetts General Hospital. Early in January, 1926, Dr. Mixter performed a partial



Case S-326. After operation.

trans-sphenoidal hypophysectomy, removing a considerable portion of the posterior lobe. Early in March the patient returned to us, having made an uneventful convalescence. Another study (B-475-a) showed a normal anterior, but apparently a still hyperactive posterior fragment. The hyperglycaemia and glycosuria were found to be present. Dr. Ulrich resumed contact with the patient and carried out a series of studies on the effect of insulin, already referred to. The patient is still under observation. There has been what seems to be a progressive upward trend to the functional activity of the anterior lobe, while the posterior fragment retains its overactivity. At the time of writing (April, 1928), the patient is having a fresh study, the results of which are not yet available. It may be said in passing that the possibility of other factors having entered the case has not been overlooked, though, as they are shortly to be considered fully, they need not be discussed here.

CONCLUSION

A paper of this type cannot be briefly summarized. It may be stated that a long series of cases have been diagnosed on the basis of certain formulas established by extensive preliminary studies already discussed (1).

Specific glandular therapy administered in strict accordance with the diagnosis as established has been shown to be efficacious in a large number of patients, producing both an amelioration of the clinical symptoms and a complementary normalizing of those laboratory findings upon which, in part, the diagnosis was based.

It seems but fair to add that while the material for this presentation is drawn in largest part from earlier cases in the series, the later results confirm and substantiate in no uncertain manner the conclusions here offered.

It is impossible for the authors to render adequate thanks to the large group of colleagues and associates who have made such vital contributions to the studies here presented. To them is due a large part of the credit for whatever merit may be found in this work.

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STUDIES OF THE ENDOCRINE GLANDS
III. THE THYROID

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PART I

In a recent publication (1) the authors have discussed the results obtained from the study of a group of pituitary cases by the application of a general method of diagnosis, the details of which have recently appeared (2). This present communication deals with the findings in a series of cases presenting some phase of thyroid disease as the principal etiological element. As the establishment of criteria of performance and methods of approach have been discussed in detail in the earlier papers, attention may be directed at once to the present thesis.

INTRODUCTION

With the sole exception of the pancreas and its endocrine malfunction producing diabetes, no one of the proven ductless glands has been so thoroughly and successfully studied as has the thyroid.* The early recognition of the association of the two classic syndromes, exophthalmic goiter and myxedema, with aberrant function of the gland, is a most important factor. Even more important has been the development of an unimpeachable surgical technique for the control of hyperfunction, and equally, the demonstration of the efficacy of preparations of the gland to correct lowered activity by a replacement therapy. The preparation by Kendall (3) of a single substance capable of duplicating in large measure the pharmacologic action of the glandular extract, is the latest step in the development. In advanced Graves' disease, long-standing myxedema, or well-established cretinism, the several pictures presented conform so nearly to the classic type that diagnosis is relatively simple and certain. In incipient or even intermediate stages, however, many cases present which may not be accurately traced to a thyroid malfunction. Further, in a not inappreciable number of individuals, thyroid disease may present a chain of symptoms utterly at variance with the classic types, and these will certainly escape proper diagnosis if only subjective findings are considered. Two pitfalls, grave at least for the patient, must sedulously be avoided. In many metabolic disturbances, end results in the form of symptoms may be suggestive of thyroid malfunction. To confirm these indications by a single test—the basal metabolic rate—and by its sole authority to establish a diagnosis, is an entirely unwarrantable procedure. Several non-endocrine conditions simulate one or another form of thyroid disease and may even exhibit a seemingly characteristic change in the metabolic rate. Differential diagnoses can be established only after complete and diversified study of the case, interpreting subjective evidences in the light of objective facts.

The endocrine glands are among the important regulators of metabolism. It is not remarkable then that disturbance of two wholly unrelated foci of control may produce a common end result. The cheery optimism of the speculative endocrinologist who sees a definite endocrine element in some obscure condition because of a single symptom also associated with some classic endocrine syndrome, does not make for progress. That many hypothyroid subjects exhibit obesity, does not connote a thyrogenic origin of all obesity. Due tribute must be paid to what may be euphemistically designated as a hearty appetite, to say nothing of the several pathological obesities in which the thyroid has no part. The promiscuous and injudicious use of thyroid extract to combat this conditions has, like King David, slain its tens of thousands. The presence or absence of thyroid enlargement is absolutely no criterion. Severely toxic and practically inert thyroids of normal size are observed daily, while the massive hyperplasias of the endemic goiter frequently are associated with a completely normal bodily function. The tale could be lengthened indefinitely, but enough has been said to indicate that the diagnosis of atypical, incipient, and obscure thyroid conditions requires a most careful and complete differential survey. The exclusion of non-endocrine disorders is no less important than the inclusion of an hormonic aberration, and should precede it.

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*This statement does not imply a failure to recognize the vast amount of animal experimentation involving the suprarenal bodies. So much of this work, however, is inapplicable to human problems involving these glands that, in this restricted sense, the above statement is felt to be warranted.

As is patent from the character of the data, and as has already been stressed (2), the presentation, in collected form, of data inherently self-contradictory, offers difficulty. Averages can be employed only when the composing units have the same sense and differ only in magnitude. An average composed from a judicious selection of + and — observations, could only present a wholly misleading normality. On the other hand, case series must be of sufficient length to merge individual differences of extraneous origin and indicate the true trend of the observation. For purpose of clarity in presentation and waiving the nice points of an ever active controversy, in the following discussion we shall designate as "hyperfunctional" (+) all cases presenting a uniform picture of what is generally regarded as an over-activity. Conversely, "hypofunctional" (—) cases present the antitheses of the foregoing. The intermediate group, in which are merged individual symptoms portrayed by the two extreme conditions, we shall designate as "dysfunctional" (±). In this later group are to be found those cases in which an initial hyperactivity is undergoing a functional involution (transition states) with an unequal rate of recession of the several salient characteristic features. In taking this position, we hope to avoid argument that can only obscure the principal aim of the thesis. Incidentally, this attitude is a not uncommon one among the serious workers in this field.

OBSERVATIONS

Following a practice established in the earlier papers, first consideration will be given to the physical measurements of the several groups. The data are collected in Table I.

TABLE I

Physical Measurements

		Gland Function			Grand
Observation	Unit	—	±	+	Average
Number of Cases		**126**	**53**	**21**	**200**
Sex—Male	%	**29**	**17**	**33**	**27**
Female	%	**71**	**83**	**67**	**73**
Age—High	Years	74	66	70	
Low	Years	8	8	18	
Average	Years	**37**	**33**	**44**	**37**
Height—High	cm.	189.5	181	176	
Low	cm.	134	131.5	148.5	
Average	cm.	**164**	**159**	**165**	**163**
Sitting Height—High	cm.	97	93	93.5	
Low	cm.	71.5	73.5	80.5	
Average	cm.	**87**	**85**	87	86
Sitting Height Index		**0.530**	**0.535**	**0.527**	**0.531**
Chest—High	cm.	150	99	93.5	
Low	cm.	57	64.5	62.5	
Average	cm.	**83**	**77**	**78**	**81**
Weight—High	kgm.	156.6	100.0	73.8	
Low	kgm.	30.6	31.3	40.8	
Average	kgm.	**65.1**	**59.5**	**58.7**	**62.9**
Area—Average	sq.m.	**1.71**	**1.61**	**1.65**	**1.68**
Lung Volume—High	cc.	5380	3720	4600	
Low	cc.	1100	1350	820	
Average	cc.	**2840**	**2570**	**2310**	

The allocation of cases to the several groups offers a statistic that is potentially misleading. The cases here presented were seen in the course of a consulting diagnostic service. Hyperactivities of the gland are usually too well defined to require elaborate analysis for diagnosis. Our studies on this group lack certain of the tests comprehended in the usual case analysis, and for this reason have been omitted from the tables including them. The relative proportion of dys- and hypo-functional cases to each other is probably more representative.

The dominant incidence of thyroid disease in the female has been noted by many (4, 5), the Mayo Clinic reporting 85 per cent females in nearly three thousand cases, while Sattler's compilation shows an equal (82 per cent) incidence. The same general trend is manifest in the hypo-functional group, though sex disparity is much less in the hypothyroidism of childhood. The age averages possibly show the tendency for the hypofunctional condition to occur earlier in life, but the lower average age of the dysfunctional group (containing many transition cases) is inharmonious. With thousands instead of hundreds of cases these discrepancies would probably disappear. The practical elimination of young cretins from this series certainly raises the average age of our hypofunctional group. This same factor undoubtedly operates in fixing certain of the other measurements, notably the standing height, at the relatively normal levels observed. In fact, our data are to be regarded as giving a picture of the incidence of thyroid disease in adult life when certain of the growth inhibitions are no longer operative. The weights here recorded, on an average, do not indicate the dominance of obesity usually associated with decreased function. The inclusion of a number of the thin amyxedemic thyroid failures—a syndrome identified by us and to be described later in this paper—unquestionably influences the average and renders it less representative of the classic type. The extremes observed for the several measurements are significant, and it is perhaps pertinent, in the light of the foregoing, to call attention to the fact that both the highest and lowest absolute values are found in the hypofunctional group. In some instances, relative exceed absolute values in significance, and in the next table are given the weight-chest-lung volume comparisons made under conditions outlined in the first paper.

Over one-third of our outspoken thyroid failures are underweight, although in deriving a net average for the group they are completely absorbed. These several net averages show a tendency from group to group, as do the relative percentages of the moieties of each above and below the predicted values. The chest measurements give no evidence of the characteristic distribution of weight, although, as has been shown earlier, the female chest-hip ratio exhibits significant differences.

The average thyroid subject shows a loss of lung volume from the predicted level which is truly significant. Bryson's (6) observation that chest expansion is limited, may bear upon this finding. That it is not solely due to fatty infiltration, as claimed by Askanazy (7), is demonstrable by comparison with the obese of other than thyroid origin. The full magnitude of the deviation in many cases is somewhat obscured in our averages by the inclusion of a significant number of incipient cases. A marked loss (40 to 60 per cent) of predicted lung volume is a common finding in cases offering no other cause for the phenomenon than the thyroid disease.

TABLE II

"Vital Capacity"

		Gland Function			Grand
Observation	Unit	—	±	+	Average
Weight—High	%	+247	+78	+27	
Low	%	—38	—29	—25	
+ Average	%	+23	+19	+13	
%	%	64	56	43	
— Average	%	—14	—11	—14	
%	%	36	44	57	
Net Average	%	+10	+6	—3	+7
Chest—High	%	+96	+26	+17	
Low	%	—21	—15	—23	
+ Average	%	+12	+11	+7	
%	%	64	47	62	
— Average	%	—7	—6	—12	
%	%	36	53	38	
Net Average	%	+5	+2	±0	+4
Lung Volume—High	%	+19	+25	+6	
Low	%	—70	—47	—75	
+ Average	%	+6	+13	+6	
%	%	11	8	5	
— Average	%	—25	—25	—41	
%	%	89	92	95	
Net Average	%	—22	—22	—39	—24

Such urine findings as may be offered in tabular form are grouped in Table III.

The urine volume has a somewhat downward tendency, and the total elimination in the hypofunctional group tends to be inadequate. Coupled with this is a high incidence of small amounts of albumin and, as will be seen later, a blood picture suggesting retention. To these general indices we have applied the term "pseudonephritis," as other signs of kidney impairment are wanting and both the blood and urine picture attain to a continued normality under treatment. Falta (8) comments on the small volume and slight albuminuria, and ascribes them to nutritive disturbances of the kidneys. Another possible explanation might be a deposition of the mucin-like substances that have been identified in other parts of the body and in the kidney by Halliburton (9) and others. Broadly speaking, lowered elimination, slight albuminuria, and not infrequently the appearance of casts, is generally recognized as of relatively high incidence in the several forms of thyroid disease. Our own figures would seem to indicate a tendency toward their appearance with failing thyroid function.

TABLE III
Urine Measurements

Observation	Unit	Gland Function			Grand Average
		—	±	+	
Volume—High	cc.	4350	3090	2060	
Low	cc.	340	360	470	
Average	cc.	**1090**	**1050**	**1090**	**1080**
Spec. Grav.—High		1.036	1.036	1.028	
Low		1.002	1.007	1.007	
Average		**1.019**	**1.021**	**1.019**	**1.020**
Albumin	%	**29**	**25**	**11**	**26**
Casts	%	**16**	**21**	**11**	**17**
Sugar	%	**7**	**17**	**16**	**11**
"Urobilinogen"*	%	**5**	**3**	**0**	**4**
Amylase Index—Av.		17	15	—	
Salol—Av.	min.	**103**	70	—	**91**
Urea Curve—Normal	%	67	70	—	**67**
Delayed	%	4	20	—	**8**
Progressive	%	4	0	—	**3**
Low	%	25	10	—	**22**
Phenol-Sulphone-Phthalein, 2 hour Elimination—Av.	%	**53**	**57**	**59**	

*Positive tests due to concomitant liver involvement. See text.

The question of glycosuria is a moot point and one that even today is far from a state of general agreement. As early as 1907 v. Noorden (10) commented on an occasional appearance of sugar in the urine of myxedemics—this, too, in a condition generally recognized as raising the sugar tolerance. Falta (8) cites a personal observation at some length of a myxedemic who showed slight alimentary glycosuria even after treatment had been suspended for two months. He infers simultaneous pancreatic involvement, also a possible complicity of the hypophysis, and offers this explanation to account for the same carbohydrate anomaly as reported by several other observers. Blood sugar values are lacking. Several other explanations offer themselves as being, at least, equally plausible. First, if it be conceded that the thyroid exercises any control over carbohydrate metabolism—and this is scarcely a debatable point—it must be remembered that many cases are seen of patients in a transition state between an earlier hyper- and a final hypo-activity. As all of the functional disturbances characteristic of the first state do not recede with the same velocity, a picture inevitably results which lacks the definition of either of the initial or terminal phases and includes features of both. A full discussion of this question is shortly to appear elsewhere, and in the interest of brevity will here receive no further mention. A second possibility in Falta's case, as well as others simulating it, lies in his report of an earlier jaundice. Scattered through the literature are occasional references to liver disorders complicating thyroid disease. We shall discuss such a group in a subsequent portion of this paper. It is well known that certain types of liver involvement lower the sugar tolerance to a very appreciable degree. Frankly, in Falta's case the liver would have to be excluded before credence could be given to the complicity of a multiglandular concert.

TABLE III-a

		Basal Met.	Gal. Tol.	Blood	Remarks
No.	Sex	Dev.	Dev.	Sugar	
B-169	F	—20	±0	102	
234	M	—11	±0	92	Earlier thyrotoxicosis (Goiter).
267	F	—10	+25%	94	Earlier thyrotoxicosis (Goiter).
528	M	—29	±0	100	Psychosis (manic depressive).
559	F	—26	±0	83	Obesity.
S-531	F	—13	—	83	Pregnant. Had been under intermittent Thyroid medication for years.
640	F	—21	Incomplete Not < N	104	Otosclerosis.
685	F	—16	±0	133	Blood sugar level due to emotion. Patient nervously very unstable, which fact probably influenced the observed basal rate to some extent.
1013	F	—26	Incomplete Not < N	100	Sterile. Became pregnant after thyroid medication.

In the present instance, because of the diversity of opinion on this point, a further analysis of the anomalous cases may be permitted. This can be confined to the pure hypofunctional group, as the anomaly really exists only with its composing members. The significant facts can be offered most compactly in tabular form.

Of the nine cases presenting, three subjects, namely, B-234, B-267, and S-531, can at once be eliminated as the first two have histories of earlier hyper-activity, and the third is pregnant. The first two are included in the hypofunctional group as the glycosuria represents the only departure exhibited, and the residual picture was clear-cut thyroid failure. The other six cases all show normal blood sugar levels and a galactose tolerance that in no case is below normal. True, the metabolism of galactose varies in some measure from that of glucose, and the urine sugar is presumably the latter. In any case, there is nothing here to support either a pancreatic or hypophyseal complication. In all of the "B" cases the liver is ruled out by other observations, and in the "S" cases, by the implication of the normal sugar tolerance. As before stated, this question will be discussed elsewhere under more elastic space conditions.

TABLE IV

Nitrogen Partition

			Gland Function			Grand
Observation		Unit	—	±	+	Average
Total Nitrogen	Av.	gms.	8.32	8.59	8.79	8.44
Urea Nitrogen	Av.	%	78.6	80.5	78.0	79.1
Uric Acid Nitrogen	Av.	%	2.6	2.1	2.2	2.4
Ammonia Nitrogen	Av.	%	4.0	3.8	3.9	3.9
Creatinin Nitrogen	Av.	%	4.3	4.4	3.6	4.3
Residual Nitrogen	Av.	%	10.5	9.2	12.3	10.3
%=or < 9%		%	64	54	67	61

"Urobilinogen," the probably non-specific response to the paradimethylamino benzaldehyde reagent of Ehrlich (11) was demonstrated only in cases exhibiting a concomitant liver disturbance. This will be discussed later. The urea curves synchronize well with the earlier evidences of loss of renal integrity which, however, the phthalein test fails to support. That this latter test is subject to many sources of error is recognized. Further, in the lowered permeability in many of these cases there is not the loss of renal function that certain of the tests would imply. The delayed elimination of salol falls in this category rather than in that of a lowered gastric motility.

A complementary observation of urine composition comes in the determination of the formula of nitrogen distribution.

The average nitrogen elimination is low, both in comparison with other endocrine and with non-endocrine disorders. As these data represent typical 24-hour collections on the patient's usual diet, and not nitrogen metabolism experiments, they cannot be equated directly with the careful studies of Janney and Isaacson (12). They would certainly seem to confirm the latter's contention in regard to the rate of protein destruction in thyroid disease. If relative weights are considered, these data offer no support of Forschbach's (13) contention that the creatinin elimination is decreased in hyper-active states. The accuracy of this has previously been denied by others.

The relation of the other measured quantities accords well with accepted normal standards. Only the residual portion departs from convention, and that registers a level definitely superior to the established norm. Moreover, this increase is shown by three-fifths of the entire group of cases. That it is not due solely to the presence of creatin, as noted by McCrudden (14) and others, has been observed by one of us (15). Rather, there exists nitrogenous material of unknown composition which is demonstrable not only in the endocrinopathies, but in other pathologic conditions as well. Of the entire group of endocrine disorders, the thyroid shows the generally highest level of this quantity, both in average amount and frequency of incidence of fractions exceeding the conventional normal. It constitutes an important datum in the general compilation of facts leading to diagnosis.

Earlier in the paper we have spoken of the pseudonephritis frequently observed in cases of thyroid failure. The urine findings have already been discussed; the blood chemistry next claims attention.

Inspection of the average values given above would not seem to confirm the statement that the blood gives evidence of retention. Two points, however, must be borne in mind. First, the level of protein metabolism in these cases is low as gauged by the total nitrogen of the urine. In the light of careful metabolism studies, among others of Boothby and Sandiford (16), and Janney and Isaacson (12), this would seem to be due to diminished intake and absorption rather than to any characteristic change in the catabolic phase. It is demonstrable that low protein metabolism lowers levels of blood nitrogen, just as high utilization determines increase. The blood picture, however, varies within much narrower limits than may be conditioned by the protein exchange.* Second, individual cases showing relatively high values lose their identity when merged by averaging with a number of observations which do not exhibit the condition. The significance of relative values should be stressed. A non-protein nitrogen of 35 mgm., absolutely normal by accepted convention, is relatively high for an individual excreting less than 6 grams of nitrogen in twenty-four hours. Further, one-fourth of the cases of this series showed values for non-protein nitrogen in excess of 35 mgm., paralleled by an almost equal incidence of urea nitrogen values in excess of the conventional norm. Fifty cases showed uric acid equal to or above 4 mgm., but of these, eighteen gave other evidences of true nephritis and are deleted in the tabular presentation. The contention, then, has a measure

TABLE V

Blood Chemistry (and Serology)

		Gland Function			Grand
Observation	Unit	—	±	+	Average
Non Protein Nitrogen	Av. mgm.	**31**	**33**	**29**	**31**
%> 35 mgm.	%	28	30	6	25
Urea Nitrogen	Av. mgm.	**16**	**15**	**15**	**16**
%> 17 mgm.	%	23	18	20	22
Uric Acid	Av. mgm.	**3.6**	**3.4**	**3.6**	**3.5**
Net[1] %= or > 4 mgm.	%	20	14	22	19
Creatinin	Av. mgm.	**1.4**	**1.5**	**1.5**	**1.4**
Residual Nitrogon	Av. mgm.	**13.2**	**16.3**	**12.2**	**15.3**
Sugar	Av. mgm.	**96**	**102**	**97**	**97**
% > 120 mgm.	%	1	6	5	3
% < 80 mgm.	%	6	0	11	5
+Wassermann	%	0	0	5	0.5
+Kahn (presumptive)	number	0	0	0	
+Spinal Fluid	number	1[2]	0	0	1
+Schwartz-McNeil	number	0	0	0	

[1] All demonstrated cases of nephritis and gout have been deleted.
[2] Non-luetic.

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*One of us (Rowe and Walker, unpublished data,) has produced changes of blood nitrogen of the order of 15-20 per cent in normal subjects by adding from 100 to 200 per cent of additional protein to a maintenance ration.

of reason when due allowance is made for the limitation of this form of presentation.

A point of interest, for which we can offer no explanation at present, is the somewhat low value of the residual nitrogen in the terminal groups. The somewhat high value of the dysfunctional cases brings the total average to a normal value.* Of the several blood constituents, the sugar is the only one which has received any extended record in the literature.

This is presumably due to the influence of the thyroid on carbohydrate metabolism and the general use of the sugar curve method to determine tolerance. Sharp differences of opinion as to the fasting level of blood sugar and the complication introduced by comparison of fasting levels with those resulting from sugar alimentation, has stimulated study, albeit, in some instances, of a somewhat uncritical character. Without detailed analysis of the somewhat diffuse literature, it may be said that a careful survey would seem to indicate no hyperglycaemic effect of thyrotoxicosis in man, and, equally, a slight hypoglycaemic tendency in thyroid failure. The figures given above show that the averages of all three groups conform straitly to the conventional normal. This is even more strikingly illustrated by a selection of extreme cases drawn from the above group and collected in Table V-a.

TABLE V-a

Blood Sugar Levels

Observation			Hypo-function	Hyper-function
			—	+
Number of Cases			24	7
Basal Metabolism Deviation—	High	%	—30	+87
	Low	%	—50	+44
	Average	%	—36	+65
Blood Sugar (fasting)—	High	mgm.	115	108
	Low	mgm.	71	78
	Average	mgm.	91	92
Number below 80 mgm.			5	1

Inspection of the figures given above fails to demonstrate any specific thyroid influence on blood sugar levels. True, these selected averages are lower than those of the entire groups, but it must be remembered that these cases represent the maximum of nutritional disturbance and hence a lower nutritional level. Not impossibly, a failure to take due cognizance of the importance of the level of nutrition prior to a sugar test is responsible for some of the conflicting data elsewhere reported. Faulty technique is another definite factor. The cases here recorded were, in the main, on a liberal, standardized diet for a period of at least four days before the blood sugar levels were determined. Further, only morning fasting bloods were taken, the foodless interval approximating fifteen hours.

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*Calculation of a large number of analyses of normal bloods would fix 15 mgm. as a fair average with a ± variation of perhaps 2 mgm. On this basis all of the values fall within the normal range.

Reverting to Table V, it will be noted that one of the hyperthyroid subjects gave a positive Wassermann reaction. The case was one of well-marked, typical exophthalmic goiter, with all of the classic signs. The luetic element here is concomitant only as affecting the general picture. In a second patient, the positive spinal fluid gave a gold curve of the meningeal type. No luetic element could be demonstrated or elicited.

In contradition to the blood chemistry, numerous observations exist on the influence of thyroid disease on the blood morphology. The earlier reports tend to stress an anaemia in Graves' disease, leucopenia and an increase in the lymphocytes and monocytes at the expense of the neutrophilic elements. Likewise, descriptions of the myxedemic picture reiterated the anaemia, leucopenia and lymphocytosis. Later observers have failed to confirm these findings in their entirety, and in several points there still exists a marked difference of opinion. In the first instance, Plummer (17) in a long series has failed to confirm the monocyte increase and the leucopenia. There is a slight anaemia, tendential rather than established, and a moderate relative leucocytosis. Our own data are assembled in Table VI.

In all of the groups the values for haemoglobin and erythrocytes are normal, although tending downward. Lymphocytosis is found throughout, although the distribution is opposite to that observed by Falta, who found it more pronounced in the hyper-active cases (8).

Likewise, the eosinophilia recorded by him is not manifest, nor do the monocytes exceed the limits of normality. While it is generally recognized that the blood picture does not correlate with the severity of the condition, an analysis of the same group of extreme cases, collected in Table V-a, may not be devoid of interest.

These values equate well with those of the preceding Table (VI), although slight differences are apprehensible. The anaemic tendency is slightly more marked, the leucocytes are slightly lower, and the monocytes and lyphocytes higher in the hyperactive group. Barring the monocytes, our figures agree well with those of Plummer, which carry conviction, as they are based upon nearly one hundred times as many cases. With the hypoactive cases, the leucocyte value is even more normal, the lymphocytes go to a slightly higher level, the monocytes remain unchanged. A slight increase in eosinophiles brings this point more nearly in accord with Falta's observations, but falls far short of the really significant magnitudes recorded by him.

TABLE VI
Blood Morphology

Observation		Unit	Gland Function —	±	+	Grand Average
Haemoglobin	Av.	%	**87**	**87**	**88**	**87**
Erythrocytes	Av.	10^6	**4.84**	**4.87**	**4.94**	**4.87**
Color Index			0.90	0.89	0.89	0.90
Leucocytes	Av.	10^3	**7.5**	**8.2**	**7.2**	**7.7**
P. M. N. Neutrophiles	Av.	%	**56**	**57**	**60**	**57**
%=or > 75%		%	2	12	5	
Lymphocytes	Av.	%	**38**	**35**	**33**	**37**
%=or > 33%		%	66	54	43	60
Eosinophiles	Av.	%	**2**	**2**	**2**	**2**
Net %=or > 3%[1]		%	19	27	11	20
Monocytes	Av.	%	**4**	**6**	**5**	**4**

[1] Cases in which a non-endocrine cause of eosinophilia was demonstrated have been deleted.

TABLE VI-a

		Hypofunction	Hyperfunction
Haemoglobin	%	87	84
Erythrocytes	10^6	4.71	4.59
Leucocytes	10^3	8.0	6.7
Neutrophiles	%	52	55
Lymphocytes	%	41	37
Eosinophiles	%	3	1
Monocytes	%	4	7

Seemingly, the lymphocytosis is the only point of real departure from the generally accepted normal adult picture, and this is found in practically all of the endocrine states and in not a few non-endocrine disorders. The magnitude of the relative increase is somewhat greater in thyroid than in the other named conditions.

The respiratory metabolism and its usual expression in the basal metabolic rate, constitutes a chapter of the greatest importance in the diagnosis of thyroid malfunctions. Taken as a sole criterion, usually it is wholly inadequate to establish a diagnosis; considered as one observation in a group, it probably has more individual significance than any other single test, with the possible exception of the sugar tolerance. And this statement presupposes a careful and complete clinical analysis of the case as intrinsic in any diagnostic procedure.

From the initial observations of Magnus Levy (18) that thyroid disorders were associated with marked changes in the oxygen consumption, an extensive literature has come into being. In the interest of brevity, no attempt will be made to review the earlier work; the discussion will be confined to our own observations, since they constitute a part of the general diagnostic scheme. The data are found in Table VII.

Following the convention earlier defined, we find the uncomplicated hypoactive states showing an oxygen consumption rate equal or inferior to 10 per cent below the predicted value. Similarly, the established hyperfunctional cases range from +19 to +87 per cent. The points of emphasis lie in the direction of the change, and more importantly in the amount. While other disorders may condition significant changes, but few approach in magnitude those of thyroid origin. And with these—diabetes with great emaciation and Addison's disease on the one hand, and the leukaemias and high fever on the other—a few relatively simple additional observations will permit of a ready differentiation. As has been discussed elsewhere (2) of the endocrine concert, only the adrenal approaches the level of myxedema in its failure, and even here it falls appreciably short of the low levels which severe thyroid inactivity can engender. While the lowest level recorded in this series is —50 per cent, we have recorded cases falling nearly 10 per cent lower. A few similar observations have been recorded by others.

The blood pressure values show a definite gradation in the sense of the basal rate. The picture in the hypothyroid group is complicated by the fact that in the later stages arteriosclerosis tends to raise blood pressure from the initial low to a final hypertensive level. In any average such as the present, which includes all chronological phases, a few arteriosclerotics will raise the average appreciably. This is well illustrated in the sequence of the percentages of low values for the systolic pressure. As is to be expected, the diastolic readings are less influenced. The pulse rate sequence is also striking and of the order to be expected. Very slow heart rates are usually associated with established failures, although with mounting blood pressure there is a tendency for the pulse to augment. These trends do not synchronize, however, and constitute one of the several elements leading to the contradictory picture of the transition state. The rapid breathing, frequently concomitant with the tachycardia of Graves' disease, finds tendential expression in the values given above. Likewise, the hypothermia of the established failure is

TABLE VII

Respiratory Metabolism

Observation		Unit	Gland Function			Grand Average
			—	±	+	
Basal Metabolism Deviation	High	%	—10	+18	+87	
	Low	%	—50	—31	+19	
	+ Average	%	—	**+11**	**+42**	
	%	%	0	19	100	
	— Average	%	**—24**	**—14**	—	
	%	%	100	81	0	
	Net Average	%	**—24**	**— 9**	**+42**	
	% > +10 %	%	0	6	100	
	% between +10% & —9%	%	0	39	0	
	% = or < —10 %	%	100	55	0	
Blood Pressure:	Systolic Av.	mm.	**114**	**120**	**138**	
	% < 110 mm.	%	54	32	10	
	Diastolic Av.	mm.	**71**	**74**	**70**	
	% < 65 mm.	%	33	26	50	
Pulse Rate:	Av.	Per min.	**66**	**79**	**101**	
	% = or < 80 per min.	%	8	45	81	
	% = or > 70 per min.	%	70	21	0	
Respiration Rate:	Av.	Per min.	**15**	**16**	**18**	
	% = or < 10 per min.	%	9	4	10	
Temperature:	Av.	Deg. F.	**97.7**	**98.2**	**98.2**	**98.0**
Alveolar CO_2:	Av.	mm.	**39**	**38**	**37**	**38**
	% > 35 mm.	%	78	65	67	74
	% = or < 30 mm.	%	5	8	14	7

indicated. It must always be borne in mind, as earlier noted, that in any compilation such as the present, the extreme findings of the terminal state are minimized materially by the inclusion of the incipient and developing cases. Trends, therefore, take on an added significance.

The prevailing tendency of the alveolar CO_2 tensions is toward the normal. The sub-normal tensions observed are possibly influenced by the measure of the patient's co-operation,* and in the over-active cases rapid breathing may condition some CO_2 deficit. The Fredericia method was used throughout, earlier study (19) having demonstrated its relative dependability. Failure to expel the air thoroughly will give a sample diluted by the tidal phase.

TABLE VIII

Galactose Tolerance

		Gland Function		
Observation	Unit	—	±	Average
Male				
Dose: High	Gms.	40	30	
Low	Gms.	30	20	
% above normal	%	13	0	
Average deviation of dose	%	+33	—	+33
% equal normal	%	87	33	
% below normal	%	0	67	
Average deviation of dose	%	—	—33	—33
Female				
Dose: High	Gms.	60	40	
Low	Gms.	40	20	
% above normal	%	33	0	
Average deviation of dose	%	+31	—	+31
% equal normal	%	67	63	
% below normal	%	0	37	
Average deviation of dose	%	—	—29	—29
Summary				
% above normal	%	25	0	18
% equal normal	%	75	56	69
% below normal	%	0	44	13
Average + Deviation (1)	%	+32	—	
Average — Deviation (1)	%	—	—31	

(1) Not weighted for relative number of cases.

The last laboratory observation to be considered, the sugar tolerance, equates with the basal rate in diagnostic importance—and is equally unfitted to be a sole and final arbiter.

For reasons which have already been discussed, galactose was selected as the vehicle for the tolerance test. That it undoubtedly has a different metabolic cycle from glucose may be freely admitted. The chief aim was, however, to devise a sugar tolerance test which should be simple, easily applied, and, most importantly, clear cut in its indications. That galactose complies with these criteria has been amply demonstrated, while the intrinsic differential sex influence is an added advantage of great value. The majority of observations of sugar tolerance are based on glucose studies, and the greater part of these on the blood sugar curve method. As one of us (20) has shown, the so-called diagnostic curves of hyper- and hypo-thyroidism are readily reproducible in a group of established thyroid failures, or equally with normal subjects, by the use of dosages above or below the utilization capacity of the given individual. For example, Olmstead and Gay's (21) two differential curves were reproduced by us in a single group of myxedemics by the use of sub- and supertolerance doses. The shape of the blood sugar curve is determined by the relation of the dose given to the individual tolerance, and at the best is but qualitative in its indications. The lack of dependence of the reaction to the test meal upon body weight has been stressed. For example, if the Janney and Isaacson technique (22) were followed in case of myxedemics whom we have studied and who were identical in all respects except body weight, one would have received 84, the other 218 grams of glucose. As it was, one responded to 40, the other to 50 grams of galactose. The curves elicited by test meals based on weight could not fail to be misleading in any quantitative sense.

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*In a few cases it was possible to demonstrate this element.

The inclusion of quantities of other foods and of the juice of grapes or the citrus fruits is so patently undesirable as to require no discussion.

Review of the literature shows a variety of contradictions, but in the main it may be said that in existing hyperthyroidism the sugar tolerance is diminished, while the reverse obtains with the opposite terminal condition. Definite quantitative expression is usually lacking. Hirschl's (23) report of the failure of 500 grams of glucose to excite glycosuria in a group of myxedemics, equates with some of Miura's (24) observations. The interest here is in the physiological phenomenon of the retention of these massive doses rather than in a quantitative significance of the test.

Of tests with galactose, but few are recorded. Bauer (25), using 40 grams and requiring for his standard an elimination in excess of 3 grams, found two positive in nine cases of hyperthyroidism. Wagner (26), with the same dosage but positive response indicated by one gram, reported thirteen out of fourteen as positive. Strauss (27), with 30 grams, and Hirose (28), with 25, both using a qualitative urine test as the criterion of response, found, respectively, three in four and nine in nine to be positive in thyrotoxicosis. Neubauer (29) tested a group of cases after thyroidectomy, using 40 grams and an elimination greater than 0.9 grams as the criterion. Thirty-eight out of forty-five were positive, and only two failed to show some sugar.

Our own findings agree in sense with the foregoing, but differ widely in the quantitative expression. For reasons given in the table, no established cases of hyperthyroidism appear. A few isolated records, made in connection with other studies, would seem to indicate that the established hyperthyroid case exhibits either a normal or slightly depressed tolerance for galactose, of the same order of magnitude as observed in the dysfunctional group. This statement is tentative and is open to revision should an extended series of observations indicate necessity. Present information warrants the conclusion given above. Perhaps the most striking feature of the results is the dominantly large percentage showing a normal tolerance. Further, where deviation does occur, it is of a very moderate order in the uncomplicated cases. A few of our observations have been omitted from the general tabulation, as their inclusion could only serve to mask the general trend, and in each instance the anomaly was directly traceable to a non-endocrine cause influencing carbohydrate metabolism. The cases severally were those of one male giving positive response with 20 grams (a —33 per cent of deviation), and four women averaging a deviation of —68 per cent. They were all demonstrated thyroid failures and all equally had a demonstrated liver disorder to which the lowered tolerance was directly referable. In this connection it may not be inapposite to recall the fact that the first use of galactose for function testing was by Bauer (30) in 1906, and was offered as a means of evaluating liver involvement.

To summarize then, the status of galactose tolerance in thyroid disorders: Over two-thirds of the subjects show a normal tolerance. When extraneous effects influencing tolerance can be excluded, the dose producing melituria, if altered, moves in opposite direction to the basal rate change and is always of moderate amount. These results agree qualitatively with other observations, but differ materially in the quantitative expression. The differential significance of this fact is patent.

There is yet another point in connection with the carbohydrate metabolism that may well be touched upon at this time. Earlier in the text, note was made of the occasional appearance of glycosuria in patients with demonstrated thyroid failure, seemingly uncomplicated by other factors which might influence the sugar assimilation limit. From the foregoing discussion, it is evident that the thyroid influence on carbohydrate metabolism in general is definite, but of a lesser order of magnitude than that of the pancreas, the pituitary or the adrenal. In a few cases, however, of unmistakable exophthalmic goiter, we have observed a profound influence on the assimilation limit usually associated with relatively small changes in the respiratory metabolism. The protocol of a typical case will be given and discussed in a subsequent portion of this paper. A possible explanation of the apparent anomaly could lie in the existence of a second thyroid hormone exercising an influence on sugar metabolism as does thyroxin, or its analogue, on the consumption of oxygen. This suggestion is offered tentatively; it will be discussed later in the paper.

PART II. CLINICAL SECTION

INTRODUCTION

The clinical section of this paper is based upon the analysis of a series of 100 consecutive cases which comprise part of the larger series reported in the previous section. The reasons for selecting the smaller group for clinical analysis are: First, that all the patients in it have been under the personal observation of one of us for sufficient time to demonstrate the effect of treatment, confirming the diagnosis; and, second, that the series can be fairly compared with an equal number of cases of pituitary failure already reported. All the cases reported here represent thyroid failure, as demonstrated by the laboratory findings and response to treatment. Cases of hyperthyroidism and dysthyroidism have been excluded for the sake of clearness and brevity.

SOCIAL AND FAMILY HISTORY

Social History: The social history of these patients does not yield any new information of value in regard to thyroid failure. It is nearly impossible to make a fair and accurate division as regards nationality, since the mixture of races is so complete. Also, because of the mobility of population, it is impossible to separate patients into significant groups as regards geographical factors, since many individuals have lived in, and outside of, goiter belts for varying periods of their lives. In individual cases, the patient's birthplace and residence may be relevant, but in a large series such factors are not significant. Of this series, 97 per cent gave their nativity as ''American.'' In the majority of these the names were Anglo-Saxon, with a definite minority suggesting Irish or Jewish parentage.

Sex: Division as regards sex shows that slightly over one-fourth of our patients are males (see Table I). This agrees with Biedl's (31) figures, but is rather higher than those of Dock (31). All are agreed, however, that hypothyroidism occurs more frequently in women than in men, but that the condition is not extremely rare in the latter. There is no satisfactory explanation of the fact that the female is three or four times more liable to disturbances of thyroid function than the male. It seems possible, however, that this preponderance is due to the alterations in metabolism incident to pregnancy. The female thyroid possesses a potential variation of function not demanded of the male, and this potential variation may cause the lack of stability which seems to distinguish the female from the male gland.

Age: Our figures as to age distribution differ slightly from those by Boothby (31) at the Mayo Clinic. Of his 89 cases, 73, or 82 per cent, were between thirty and sixty years of age, while in our 100 cases, only 52 per cent were between those ages, and 41 per cent were less than thirty years old. Possibly the difference may be due to the fact that Boothby's patients were ''myxedemics,'' which signifies the presence of myxedematous accumulations as one basis for the diagnosis, while our series includes all patients with hypothyroidism, as demonstrated by our examination and treatment, regardless of the presence or absence of myxedema. It may perhaps make for clearness if we state at once that in our opinion myxedema is not a sine qua non of thyroid failure, and that its presence in any patient depends, not so much upon the degree of thyroid depression, as upon coexisting circulatory and renal arteriosclerosis. Naturally, the symptom, if such be its origin, would be much more common in middle and later life than in youth, and the difference between Boothby's figures and ours becomes, on this basis, quite logical.

TABLE IX

AGE INCIDENCE

1-10 years	2%
11-20 years	19%
21-30 years	20%
31-40 years	17%
41-50 years	17%
51-60 years	18%
61-70 years	4%
71-80 years	3%

TABLE X

FAMILY AND SOCIAL HISTORY

Family Record	
Abnormal weight	8%
Abnormal height	6%
Diabetes	7%
Goiter (unclassified)	11%
Thyroid failure	16%
Acromegaly	0%

Inheritance: In nearly half of our patients there was a history suggesting endocrine disease in the family. In 27 per cent there was definite proof of thyroid disturbance, as shown by goitre or proven thyroid failure, and in 7 per cent there was a reliable history of diabetes mellitus. In some instances the family tendency was particularly striking. We have records of one family in which both father and son have undoubted hypothyroidism; in each of two other families both children are similarly affected, and in one family, consisting of father and three children (see later), all have been proven in our clinic to have thyroid failure, with basal metabolic rates ranging from —23 to —33 per cent. There can be no doubt that as Lisser (31) says, "Families may and do transmit a predisposition to disturbance of the endocrine system, just as some families exhibit a tendency to cardiovascular disease."

Marital States: Forty-three per cent of our patients were single, 57 per cent were married. The fraction of unmarried patients may possibly have the same significance that Davidoff (32) ascribes to analagous figures in his series of acromegalics, but it seems more probable that our rather high percentage of single patients is due to the effect of thyroid failure on the patient's personality, a point which will be discussed more fully later in this paper. The high incidence of sterility (22, or 39 per cent of the married group) will also be discussed under the symptoms of hypothyroidism.

TABLE XI

PAST HISTORY

Development	
A. Physical, normal	86%
Physical, abnormal	14%
Physical, delayed	9%
Physical, accelerated	5%
B. Mental, normal	94%
Mental, abnormal (delayed)	6%*
C. Sexual,†, normal	45%
Sexual, delayed	37%
Sexual, early	7%
Sexual, not stated	11%

*Four of the six showed coincident physical retardation.
†Females only. (See text.)

Physical Development: Only 14 per cent of our patients gave a history of disturbed physical development. This means that in only 14 per cent was the thyroid failure operative during the period of growth. In our experience it is only in the cretins, in whom the lack of thyroid secretion probably exists from birth, that any marked influence of the thyroid upon development is demonstrable. This is in marked contrast to disturbances of pituitary activity, which affect growth as a rule, rather than as an exception.

Mental Development: Here again our figures for delayed mental development are certainly less than the truth, but they are significant as indicating that both mental and physical development are delayed or impaired if thyroid activity be depressed, whereas pituitary hypofunction, which also gives rise to delayed growth, has a much less marked effect upon mental development. The practical elimination of cretins from our series adds weight to this statement.

Sexual Development: Onset of Puberty. Exact figures for this event can be obtained only from female patients, there being no definite occurrence to mark puberty in a boy as does the appearance of the catamenia in girls. Our figures, therefore, represent only the females in our series. It is courting criticism to attempt to set arbitrary age standards for the normal appearance of menstruation, but for the sake of definite criteria, we have chosen 12 years as the early limit and the fourteenth birthday as the late limit for normal appearance of catamenia. On this basis less than half our female patients certainly began to menstruate during the normal period, and of those whose menarche was abnormal, delay was six times more frequent than precocity. Here again the depressing effect of thyroid hypofunction on development is more clearly apparent, and it is likewise demonstrated that delayed puberty demands careful investigation of the patient's endocrine system (particularly the thyroid and pituitary), if no organic disease can be demonstrated to explain the condition. That thyroid extract will correct the delayed sexual development due to hypothyroidism was beautifully demonstrated by one patient in our clinic. Born a cretin, her condition was early recognized and efficiently treated by Dr. J. J. Thomas of Boston. She came under our observation when she entered the obstetrical ward to be confined, and her past history disclosed the hypothyroid condition. Her menarche was only slightly delayed, her catamenia had been normal, and presumably she had escaped sterility by the early recognition of her condition and its efficient treatment. If medication is to be effective, it must be instituted during the growth period. It will not suffice to "wait and see" till the patient has passed twenty and then begin thyroid medication. The opportunity has then passed for normal development of the sex organs, and the result of such tardy treatment is almost certainly failure.

TABLE XII

PREVIOUS ILLNESSES	
Mumps	47%
Tonsillitis	40%
Measles	23%
Scarlet Fever	23%
Pneumonia	15%
Diphtheria	12%
Typhoid Fever	8%
Emotional Strain	6%
Rheumatic Fever	3%
Trauma	2%
Tuberculosis	0%
PREVIOUS OPERATIONS	
Tonsillectomy	40%
Appendectomy	5%
Cholecystectomy	1%
Hysterectomy	1%
Thyroidectomy*	1%

*There are a number of cases of hypothyroidism of surgical origin in the larger series.

Previous Illnesses: It was possible to demonstrate a definite connection between previous infections and thyroid failure in only scattered instances, and it is our belief that the acute infections are not generally patent factors in the production of hypothyroidism. The incidence of definite and severe chronic tonsillar infection in these patients is, however, prominent enough to suggest that it may be an important etiological factor. Forty per cent of our patients had had repeated severe sore throats and 32 per cent had had tonsillectomy. These figures are higher than those for measles, and nearly as high as those for mumps—both extremely common infections. The further fact that physical examination showed that in 32 per cent of our series the tonsils had been removed and that in an additional 24 per cent they were definitely infected is significant of a not improbable connection between chronic tonsillar infection and depression of thyroid function. It has also been our experience that the removal of infected tonsils is a necessary preliminary step in the successful treatment of hypothyroidism. In several instances no benefit was obtained from thyroid extract pushed to the point of mild toxic symptoms before tonsillectomy, while the removal of the focal infection was followed by rapid response to a smaller dosage. It is no longer debatable that focal infection has a profound depressant effect upon bodily nutrition and function. How it produces this effect has never been determined, but it seems possible that it may be through the endocrine system and, more particularly, through a direct depression of thyroid or pituitary function.

TABLE XIII

DURATION OF ILLNESS

Less than 6 months	4%
Between 6 and 12 months	5%
Between 1 and 2 years	20%
Between 2 and 3 years	11%
Between 3 and 4 years	12%
Between 4 and 5 years	6%
Between 5 and 10 years	11%
Between 10 and 15 years	11%
Between 15 and 20 years	3%
More than 20 years	7%
"Always"	10%

Duration of Illness: The striking feature in the table showing the duration of thyroid failure in our series of patients is the long existence of the condition before it was recognized, a feature commented on by Blumer, Janney and others. To a certain extent the failure to make the diagnosis depends upon the insidious onset of the disease, and the lack of definite physical signs to account for the symptoms. In our opinion there is, however, a still stronger reason for the failure of physicians to recognize hypothyroidism. This lies in the general impression, derived from the name applied by Ord to the condition described by Gull, that there can be no really significant depression of thyroid function without the presence of demonstrable myxe-

TABLE XIV

PRESENT ILLNESS

Patient reported as a

Symptom:

	Chief Complaint	Definite Symptom
Menstrual disturbance	5%	54%
Exhaustion	59%	80%
Depression	3%	29%
Irritability	...	30%
Instability	5%	5%
Underweight	2%	32%*
Overweight	8%	21%*
Goiter	7%	14%
Deafness	5%	15%
Vertigo	4%	36%
Headache	8%	46%
Failing vision	1%	10%
Paræsthesias	4%	24%†
Insomnia	1%	16%
Appetite±	...	53%
Indigestion	3%	25%
Vomiting	1%	22%
Constipation	3	52%
Sterility	2%	39%‡
Impotence	7%	11%§
Menstrual disturbance	5%	54%
Diminished libido	3%	33%
Dyspnoæ	1%	28%
Palpitation	...	22%
Loss of hair	2%	30%

ADDITIONAL

Skin eruptions	12%
Diminished perspiration	40%
Hypothermia	41%
Marked change in weight	61%
Personality changes	63%
Loss of memory	7%
Urinary symptoms	14%

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*Observed by measurement.
†Five cases severe.
‡Of 61 married.
§Males = 27.

dema. Therefore the possible existence of hypothyroidism never occurs to the average physician when myxedema is not demonstrable. In a previous paper (33) one of us has called attention to the fact that in a series of forty cases there was no significant difference in basal rate between those cases that showed myxedema and those that did not. The difference between the two groups lay in the ages and in the presence or absence of arteriosclerosis as determined by physical examinations, blood pressure determinations, renal function tests, and urinalysis. It was pointed out that arteriosclerosis was practically the rule in patients with myxedema, and was very rare in those who did not exhibit this condition. Our present series confirms the earlier findings and gives added support to the thesis that while there is no myxedema without marked hypothyroidism, there may be marked thyroid incompetence without myxedema, just as there may be marked renal incompetence without edema. If this be the case, it would be well to drop the use of the term myxedema as synonymous with hypothyroidism, since it seems to inhibit the early diagnosis of that condition.

Presenting Symptom: Reference to the chart brings out the fact that while the chief complaints of patients with hypothyroidism are many and varied, the outstanding symptom is general subefficient bodily performance, termed variously ''exhaustion,'' ''lack of endurance,'' ''chronic fatigue,'' or ''weakness.'' This symptom is, of course, the expression of the depressed metabolic activity incident to thyroid hypofunction, and is not due to organic change demonstrable by physical examination. Superimposed upon this expression of abnormal metabolism are a varied assortment of special complaints, indicating the effect of depressed thyroid activity upon practically all the various ''systems'' that compose the body. Prominent among them stands the nervous system, and because of the prominence of symptoms referable to it, many patients with hypothyroidism have had to carry for years the added handicap of a diagnosis of neurasthenia. It is true that neurasthenia, in its literal meaning is present, but before the term is applied to a patient in its medical sense, hypothyroidism as a possible basis for or aggravating factor of the neurasthenia, must be carefully considered. The tests which prove its presence or absence are so simple that there is no justification for not applying them. The difficulty in the diagnosis of hypothyroidism lies not in the lack of a certain method of establishing it, but in the failure of the physician to consider it as a possibility in any given instance.

Whenever a patient complains of chronic fatigue or weakness, plus one or more of the symptoms enumerated in Table XIV, and physical examination fails to disclose organic disorder sufficient to explain the symptoms, that patient deserves such tests as are necessary to establish the presence or absence of thyroid or other endocrine hypofunction.

To do this, one measurement of the basal metabolic rate is not enough. There are other conditions that will depress basal metabolism, and these must often be eliminated by a combination of tests sufficient to embrace all the possibilities. As a rule, however, the symptoms enumerated, the absence of organic involvment, the presence of bradycardia, hypotension, hypothermia, changes in personality, malnutrition and abnormal weight, and the demonstration of a basal metabolic rate, properly determined, of —20 per cent or more, with an approximately normal sugar tolerance, is sufficient to establish the diagnosis and eliminate so-called neurasthenia.

Weight: This feature has already been thoroughly analyzed and deserves mention here only to emphasize the fact that underweight does not argue against hypothyroidism.

Loss of Energy: While this symptom was the chief complaint of only 59 per cent of our series of patients, it occupied a prominent place in the histories of eight out of every ten. It was variously described, but could always be translated into an expression of the inability of the patient to live a normal existence because of lack of energy to meet normal demands. This realization of subefficiency often results in the development of an ''inferiority complex'' and depression or hostility toward the world in general.

Psychoses: Definite psychosis was present in four of our patients, and in all was of the manic depressive type, the depressed phase being much the more prominent and of longer duration. Two of the four had attempted suicide; the other two had seriously contemplated it. All of them complained bitterly of their inefficiency and their inability to enjoy life. Two of the four have responded satisfactorily to thyroid medication, one is improved but still has periods of marked depression, while the fourth is incooperative as to treatment and remains depressed. The so-called "neurasthenic" symptoms of hypothyroidism respond as a rule in a most dramatic manner to adequate treatment. Within a few weeks after the metabolism has been normalized by thyroid extract the depression and incooperative attitude disappear, and the patient's entire personality undergoes a marked change for the better.

Nervous System: Beside the psychiatric manifestations, symptoms suggesting organic disease of the central nervous system were numerous and prominent in our series of patients. Frequent headaches, often severe enough to be incapacitating, occurred in 46 per cent. Vertigo, usually of moderate intensity, was present in thirty-six. In three it was severe enough to justify lumbar puncture, and in each case an abnormal spinal fluid was found. In one case the vertigo was so severe that a diagnosis of tumor at the cerebello-potine angle had been made, and operation contemplated. Futher study disclosed a low basal rate which directed attention to the thyroid, and other tests confirmed the diagnosis of hypothyroidism. The patient has now been under treatment for two years. He had only one attack of vertigo after treatment was instituted, and has had no vertigo at all during the past twelve months. No myxedema was demonstrable in this patient. The cause of the vertigo in hypothyroidism is not established, but two explanations offer themselves. The most obvious, and perhaps the simplest would be to ascribe it to cerebral anaemia, due to the slow pulse and low blood pressure characteristic of the underlying condition. This may well be the cause of the milder types of vertigo, which, by the majority of our patients were described as transient, and associated with rapid changes in posture. It would hardly explain, however, the severe attacks to which the patient mentioned above was subject, and which have also been recently described by Moehlig (34). It seems much more likely that the cause of such severe vertigo, which closely simulates Meniere's syndrome, lies in the abnormal spinal fluid which is found in severe cases of thyroid failure. Our findings in three cases have been paralleled by Ayer (personal communication) in a similar but slightly larger group, and indicate a marked departure from normal, as shown by pressure changes, the nitrogen fractions, and the gold sol curve. Further study is necessary to establish the relation of these findings to the vertigo, but the fact that Ayer has demonstrated that the fluid returns to normal under thyroid treatment makes it clear that the abnormalities are but one more manifestation of the far reaching effect of thyroid failure upon bodily function.

Deafness of the progressive, non-catarrhal type occurred in 15 per cent of our patients; in 7 per cent it was accompanied by tinnitus. This association of deafness and thyroid failure was pointed out by Falta (8), who ascribed the impairment of hearing to myxedemic changes in the eighth nerve. In most of our patients, however, no myxedema was demonstrable, and it seems more probable that the diminished hearing depends upon nutritional changes due to the thyroid failure. Whatever the local change may be, the fact that the hearing improves when the metabolism is normalized with thyroid extract leaves no doubt that the deafness is dependent, in part if not entirely, upon the thyroid hypofunction. The entire subject of progressive non-catarrhal deafness demands restudy, and two of its outstanding characteristics, *i. e.,* inheritance and exacerbation after pregnancy, indicate clearly the necessity of including examination of vital functions in such a study.

Parasthesias are common in hypothyroidism and often severe. Usually they consist of numbness and tingling. One of our patients was unable to continue her work as a cook because her fingers had become so numb that she could not handle dishes without dropping them. In another the tongue was affected, causing thick, unintelligible speech. The most common site of the parasthesias is, however, the extremities, which are often described as feeling as though they were wrapped in cotton wool. The immediate cause of these disturbances of sensation is not clear. They may be due either to nutritional changes in the nerve trunks, or to the pathological cerebro-spinal fluid. They disappear promptly under treatment.

Digestive System: Constipation and variable or diminished appetite are the outstanding digestive symptoms in this as in other series. The latter is usually ascribed to the former, but it seems possible that other factors may be operative. These will be considered below. The constipation is of the atonic type, is aggravated by a diet rich in roughage, and is resistant to treatment by cathartics. It responds readily to thyroid extract.

Biliary Tract: Because of the prominence of vomiting, indigestion, and jaundice in our patients (see Table XIV) it seemed worthwhile to study the digestive tract by means of barium meals and radiography, Graham test, and duodenal lavage in a number of cases. The results of this investigation appear in Table XV.

TABLE XV

RELATIVE INCIDENCE OF LIVER AND GALL BLADDER DISEASE

Diagnostic Evidence	Thyroid	Not Endocrine Long Form	Not Endocrine Short Form	Pituitary
	Established			
Liver Function				
+	7	12	2	4
+ +	7	9	1	3
+ + +	8	7	5	0
Graham	1	4	2	1
Operation	2	0	0	0
Jaundice (current)	1	0	0	0
Total	26	32	10	8
	Probable			
History				
Previous jaundice	5	3	1	0
Miscellaneous	3	0	2	0
Physical Examination				
Enlarged liver	2	1	0	0
Tenderness	3	0	0	0
Miscellaneous Findings	0	0	2*	0
Total	13	4	5	0
Grand total	39	36	15	8

Comparison has been made between four series of one hundred consecutive cases each, exhibiting respectively thyroid and pituitary disease, and non-endocrine disorders as determined by the "Long Form" and "Short Form" studies. The choice of the two latter depends upon the fact that because of certain studies now under way many cases are received selectively for the longer investigation in which a liver (or gall bladder) element is patent before admission. The "Short Form" group is much more representatively a cross section of the general endocrine service. Positive evidences of involvement of liver, gall bladder or both derive from the duodenal function test (McClure), positive Graham test, history of recent cholecystectomy or current jaundice. The probable evidences lie in the facts of the past history, the results of physical examination or other suggestive observations. While but single defining evidences are reported in the table, it is to be understood that the thorough general study adds numerous supporting observations. For example, a number of the positive liver function cases gave positive Graham tests, icteric indices, etc., as well as yet other positive indications.* Reverting to the table, it is patent that liver or gall bladder disease is from three to five times as common in thyroid as in pituitary disease, and more than twice as frequent as in a typical group of non-endocrine complaints. The relative parity of incidence in the "Long Form" series of non-endocrine disorders derives in part, as noted above, from the fact that this group selectively contains a number of liver cases admitted for that study.

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*One case of profound secondary anaemia without determined cause, one case showing duodenal pathology by radiography.

Biliary Function: From the tabulation it is apparent that disturbance of biliary function frequently complicates hypothyroidism. This is of possible importance in explaining the apparently conflicting findings in regard to sugar tolerance in certain patients. If the sugar tolerance suggests disturbed pituitary function, and all other findings are more consistent with hypothyroidism, determination of the biliary function by appropriate methods will often eliminate the apparent conflict.

Whether or not hypothyroidism and disturbances of the biliary tract are causally interrelated, we cannot state from the evidence at hand. It may be, however, that a diseased gall bladder furnishes the focus of infection which is the etiological factor in the depression of thyroid function in a given case, and it also seems possible that sluggish biliary function due to thyroid failure may prepare the way for various liver disturbances. The question is being intensively studied in the Clinic, and final conclusions will be reported when sufficient material is available.

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*It may not be inapposite here to state that in our opinion, the duodenal function test gives primary information about the level of liver function, while the Graham test, naturally, deals with the gall bladder. With a positive Graham, the function test is usually positive also, but a negative Graham test frequently occurs with a positive liver function test. An inference tentatively offered and awaiting confirmation by further study is that gall bladder disease is usually associated with liver dysfunction, but that the converse is by no means of as frequent occurrence.

Reproductive System: A prominent symptom in our patients was disturbance of menstrual function, not dependent on pelvic disease. The type of disturbance was characteristic. Complete amenorrhea, so common in pituitary hypofunction, was rare. Nor does the gradual lengthening of the intermenstrual interval and diminution of duration and amount of flow, likewise characteristic of that condition, occur so frequently in this series of patients. In hypothyroidism the characteristic menstrual disturbance may be characterized as loss of control. Menorrhagia is more common than diminished flow, and the intermenstrual interval becomes markedly disturbed. It may vary from ten days to three months in any given patient. Pain at onset of menstruation occurred in a few of our patients in whom the periods had never become normally established, but it is so uncommon in hypothyroidism that its presence should always suggest possible pelvic involvement.

Sterility was present in 39 per cent of our married patients. It was not always possible to determine, in this series, whether the responsibility lay with the patient or the mate, but a special investigation of sterility which we are now carrying out confirms our impression that hypothyroidism may be the sole factor in the production of a sterile marriage, if it exists in either male or female. There are in this series examples of both male and female sterility associated with hypothyroidism, and overcome by proper thyroid medication. One male patient had been married three years, no barrier to pregnancy could be demonstrated in his wife, and, except for lack of energy, he considered himself in perfect health. The full protocol is given later. His physical examination showed no myxedema present. His basal rate was —25 per cent. He was put on thyroid extract June 16; his basal metabolism was normal on (or before) August 18. His wife had a normal menstrual period August 5-9, but the next period was missed and all the normal signs and symptoms of pregnancy developed. She was delivered, at full term, of a normal babe. It is an important fact in this case that the husband showed spermatozoa of normal number and motility in the condom specimen, and that many of them were dead in the post-coital specimen. Apparently the sterility was due to low vitality of the spermatozoa, which could not survive long enough to meet and penetrate the ovum. As a corollary, a normal condom specimen cannot be accepted as positive proof of potency in the male.

In the females, sterility was as a rule due to failure of conception, and was characteristically accompanied by diminished libido. In one patient this amounted to absolute frigidity, although she had had before the onset of the hypothyroidism normal libido and fertility. In certain cases, however, the sterility is due to repeated miscarriage. An example of this is found in one patient in the series who, after the birth of her first baby, had a severe streptococcus infection of the throat. Thereafter she became easily fatigable and felt "generally below par." She became pregnant three times, but in each instance miscarried without known cause at the end of the third month. Physical examination showed some evidences of malnutrition, low blood pressure, sub-normal temperature, and slow pulse. Her basal rate was —22 per cent. She was given thyroid extract in amounts sufficient to normalize the basal rate. She is now eight months pregnant, and no miscarriage has threatened.

It seems fair to postulate that normal thyroid function in both partners is necessary for a fertile mating. Various explanations of the manner in which thyroid failure operates to destroy fertility have been advanced, most of them involving some subtle and specific interrelation between thyroid and gonad function. Such a theory seems to us unnecessarily complicated and lacking in proof. Sterility, diminished libido and menstrual disturbances are common symptoms of any disease which seriously interferes with bodily nutrition, and we believe that it is by reason of such interference that thyroid hypofunction operates to produce the symptoms referable to the reproductive organs.

Impotence: Among our male patients impotence, relieved by thyroid medication, was present in three instances. It is hard to get accurate information about this symptom, and it is probably more common than our figures indicate. Like sterility, it is simply one evidence of the malnutrition due to the disturbed thyroid function. Its importance lies in the fact that the impotence is generally ascribed to gonad failure, in the absence of other demonstrable cause, and the patient treated on that basis, with generally disappointing results. In our experience primary gonad failure, especially as a cause for impotence or frigidity, is a much rarer condition than thyroid or pituitary hypofunction.

Skin and Appendages: The value of the skin as an index of nutrition, is too often overlooked in these days of instruments of precision. This is especially true in regard to diseases of metabolism. That the skin is profoundly affected by depression of thyroid activity is indicated by the frequency with which complaints regarding its condition appear in the patients' histories (see Tables XIV and XVI). Dry, cold skin was present in one-half the series, loss of hair in one-third, thickening and scaliness in 10 and 7 per cent, respectively, and skin eruptions, usually eczematous, in 12 per cent. There is, in these patients, a typical pallid, lifeless appearance of the skin, hair and nails which should always suggest to the examiner disturbed metabolism in general and thyroid hypofunction in particular, especially if anæmia be absent or slight. It must be emphasized, however, that these symptoms are suggestive evidence only and demand much corroborative evidence before they can be regarded as diagnostic of hypothyroidism. It is perhaps noteworthy that myxedema was demonstrable in only 10 per cent of our cases, showing how frequently marked depression of thyroid function exists without this so-called pathognomonic symptom.

However suggestive of hypothyroidism the patient's history may be, a careful and complete examination is essential for two reasons. First, it serves to detect or eliminate organic disease as a basis for the symptoms. If organic disease be demonstrable, consideration of endocrine disturbances should be postponed until it has been eliminated or evaluated. Second, a careful physical examination will bring to light certain findings which in connection with the symptoms should establish a suspicion of metabolic disturbance strong enough to demand investigation of the patient's level of functional performance.

General Nutrition: Among the physical findings referred to are the various evidences of malnutrition, such as abnormal weight, either above or below the normal. A reference to Table XVI shows how common these symptoms are in patients with hypothyroidism. Evidence of poor general nutrition was present in 78 per cent of our patients, and the skin was credited with being normal in only 33 per cent. Dryness was its characteristic departure from health, but thickening, scaling, myxedematous infiltration and eruptions of which eczema was the commonest, were often combined with the dryness. The skin was cold to the touch in half the patients.

TABLE XVI

PHYSICAL EXAMINATION

Skeletal development, over	3%
Skeletal development, under	4%
More than 10% overweight	32%
More than 10% underweight	21%
Nutrition, fair	27%
Nutrition, poor	51%
Skin, dry and cold	50%
Skin, dry and scaly	10%
Skin, thick	7%
Skin, myxedematous	10%
Malar flush	18%
Hair, scanty	30%
Hair, hypertrichosis	3%
Hair, coarse and dry	28%
Tonsils, absent	40%
Tonsils, infected	24%
Thyroid, enlarged	21%
Heart, enlarged	4%
Heart, faint sounds	31%
Heart, murmurs	6%
Heart, low voltage (cardiogram)	46%*
Arteriosclerosis	16%
Hypertension	10%
Hypotension, systolic < 100 mm.	26%
Hypotension, diastolic < 60 mm.	12%
Hypotension, total	69%
Pulse rate, above 80	4%†
Pulse rate, below 70	66%†

*Only 13 cases examined in this series.
†In substantial agreement with the larger series.

Hair: The hair is apparently more resistant to the effects of hypothyroidism than is the skin, as it was judged to be normal in 54 per cent of our series. It was termed ''thin'' and ''scanty'' in about one-quarter of the patients; coarse, dry and lifeless in an equal number. Alopecia areata was prominent in one patient, complete alopecia was present in two. Excessive hair growth is a rare finding, in contradistinction to certain of the other endocrine disorders.

Focal Infection: As has been already pointed out, the incidence of absent or infected tonsils is extremely high in our patients, the former condition existing in 40 per cent, the latter in 24 per cent. In only 36 per cent were apparently normal tonsils present. These figures are significant, even in these days of enthusiastic tonsillectomy.

Thyroid Gland: Goitre was present in 21 per cent of our patients. In all, it was apparently due to simple enlargement. The importance of the finding lies in its negative value in ruling out hypofunction of the thyroid. We have seen goiter, tremor and tachycardia all present in a patient with myxedema, existing as residua of a pre-existing thyrotoxicosis.

Heart: Convincing evidence of cardiac enlargement was present in only four of our patients, and in none was the enlargement such as Fahr (35) describes as the typical ''myxedema'' heart.

Murmurs were also conspicuous by their absence, due not improbably to the lack of muscle tone in many instances. This lack of muscle tone is evidenced by the faintness of the heart sounds in these patients, and by electrocardiographic evidence of low voltage. Faint heart sounds were noted in 31 per cent of our series, low voltage in the electrocardiograms in 46 per cent of those examined. One of us (36) has previously reported the presence of this low voltage in hypothyroidism, and its disappearance under thyroid treatment.

Irregularities: No irregularities other than an occasional premature beat were noted in our series.

Pulse Rate: Bradycardia is so characteristic of hypothyroidism that the presence of the former should always suggest the latter. Sixty-six per cent of our patients had pulse rates below 70 per minute, while only 30 per cent had normal rates and 4 per cent accelerated rates. In these last, there was evidence of arteriosclerosis and true myocardial insufficiency. The lowest rate recorded in our series was 43 beats per minute. This patient's heart was apparently normal; certainly there was no heart block present.

Arteries: Sclerosis in demonstrable amount was present in 16 per cent of our patients. These included all in whom myxedema was demonstrated. Several of the patients with sclerosis were well below the age at which that condition is usually found.

Blood Pressure: Normal blood pressure existed in 21 per cent of the series. Hypertension was demonstrated in 10 per cent, accompanying arteriosclerosis and myxedema. Hypotension was recorded in 69 per cent of patients. If there be any error in measurements, it is like that of basal metabolism, practically always on the high side, so that our figures do not exaggerate the incidence of hypotension in hypothyroidism. Twenty-six of our patients registered a systolic pressure of less than 100, the minimum being 80, and twelve had a diastolic pressure under 60, the minimum being 45. That the hypotension is due to the thyroid depression is proved by the return of the blood pressure to normal in these patients under proper medication. It is not necessary to drag the adrenals into the picture to explain the hypotension.

The Cardio-Renal System: For many years it has been recognized that the typical myxedemic is prone to show evidences of degenerative changes in heart, blood vessels and kidneys. Our findings in this respect have already been presented and commented upon (33), but it seems necessary to risk repetition in order to make clear our opinion concerning the role played by cardio-renal insufficiency in thyroid hypofunction, and especially in the myxedemic form.

The majority of our patients showed no myxedema, and no definite evidence of cardio-renal disease. In a small fraction, however, myxedema was demonstrable, and in these patients certain evidence of markedly impaired circulatory and renal function, similar to that found in chronic nephritis was present. One or more of the following findings existed in every case of myxedema: albuminuria, with or without casts; nitrogen retention, as shown by the chemical examination of the blood; arteriosclerosis, hypertension, enlarged heart, or electrocardiographic findings similar to those found in myocardial degeneration. These findings we have grouped under the term "pseudo-nephritis," since they differ from true nephritis in that they are, with the exception of arteriosclerosis, and in some instances hypertension, amenable to treatment with thyroid extract. One of us (33, 37) has already pointed out the close association of this "pseudo-nephritis" with myxedema, and has expressed the belief that the latter is dependent upon the former. Until contemplated animal experimentation has furnished further evidence, we cannot regard the thesis as proven, but we wish here to emphasize the fact that evidences of cardio-renal depression or degeneration are far more common in the myxedemic than in the non-myxedemic group of patients. That the latter group should be regarded as "atypical" is, we believe, due to misconception. The fact that patients in this group are markedly underweight does not argue against this belief, for underweight is well known to exist in the most severe of all thyroid depressions, "cachexia thyropriva." The effect of normal thyroid function upon body weight is to keep it normal; in the absence of such normal thyroid activity the weight may become abnormal by either increasing or decreasing. The factors that determine the direction of its departure from normal are as yet unknown. The myxedemic patient then should be regarded as one in whom circulatory or renal insufficiency, or both, have developed on the basis of a thyroid hypofunction, giving rise to a "pseudo-nephritic" condition, but may have an equally severe depression of thyroid function.

Dysthyroidism is the term which we believe is better applied to atypical cases of thyroid hypofunction, since these patients usually exhibit symptoms of both "hypo-" and "hyper-activity" of the gland. They represent, in our belief, individuals who are examined while a previous over-activity is swinging to the underactive level, which is not infrequently its final stage. During this period of transition, certain symptoms due to the previous "hyperactivity" tend to persist longer than others, so that there exists an apparently paradoxical situation in which nervousness and tachycardia, for example, coexist with hypometabolism and other definite signs of thyroid hypofunction. Eventually such patients either become normal, or, more often, reach a definitely hypofunctional level. The interest in the condition lies in the fact that it explains some of the apparently contradictory findings in certain cases, and that it raises a question as to the advisability of immediate operation, and its extent, in mild cases of thyrotoxicosis. Our own belief is that in the absence of symptoms of cardiac embarrassment such patients should be kept under close supervision until the transition stage is past, and that the type and extent of treatment necessary can then be logically determined. If such a course is pursued, frequent determinations of the basal rate are essential, since the pulse rate, which falls far more slowly, cannot be relied on to give evidence of diminishing thyroid activity. The trend of weight and blood pressure are also important guides.

From the clinical point of view, there are many objections to regarding the estimation of the basal metabolism as a perfectly reliable method of diagnosis of, and progress in, thyroid disturbances. If it be really the basal metabolic rate which is determined, the importance of the first and subsequent readings can hardly be overestimated, but unless the operator understands thoroughly the many factors which may influence the readings, a true rate will not be obtained. We have seen, in this Clinic, a difference between the initial and final determinations of an untreated patient's basal rate amounting to 107 per cent, and varying from an abnormally high to an abnormally low value, without apparent change in the conditions of the test, and due solely to emotional factors which are often difficult of detection. We believe therefore that the basal metabolic rate alone is not a reliable criterion of thyroid activity, and that in the more obscure cases it must be supplemented by the patient's history, physical examination, and a group of other tests and examinations such as are reported in this paper.

In addition to the type of dysthyroidism described above, there is reported in the protocols below a case representative of a small group showing another class of disturbance. In them the basal rate is not altered to a degree comparable to the evident symptoms of toxicity, but the sugar tolerance, usually only slightly altered in thyroid disturbances, is markedly affected. The theoretical significance of these findings is discussed below. They are mentioned here to show that the basal metabolic rate cannot safely be accepted as the sole criterion of the level of thyroid function.

PART III—CASE PROTOCOLS

TABLE XVII

	Gall Bladder			Psychoses		
Case Number	B-467	B-480	B-845	B-875	B-528	B-35
Diagnosis	—	—	—	*—	—	—
Sex	M	F	M	F	M	F
Age (yrs.)	31	52	37	32	61	41
Height (cm.)	180	163	173	171	177	165
Weight (kgm.)	58.7	91.2	48.6	80.2	92.4	68.7
Weight Deviation (%)	−25	+45	−33	+32	+26	+15
Lung Volume Deviation (%)	+6	−52	−27	−12	−14	−46
Basal Rate Deviation (%)	−29	−36	−33	−32	−29	−50
Blood Pressure (mm.)	104/60	130/70	116/88	110/70	146/90	104/70
Pulse (per min.)	46	48	56	60	64	71
Temperature (deg. F.)	97.4	98.0	98.6	97.8	97.8	95.4
Alveolar CO_2 (mm.)	41	43	43	43	35	33
Urine Volume (cc.)	600	1290	1120	850	790	990
Spec. Grav	1.024	1.013	1.020	1.019	1.024	1.010
Albumin	0	+	0	0	0	+
Casts	0	0	0	0	0	0
Sugar	0	0	0	0	+	0
Total Nitrogen (gms.)	8.32	7.57	9.30	5.72	5.50	7.62
Residual Nitrogen (%)	14.5	8.2	6.3	9.0	9.8	6.6
"Urobilinogen"	0	+	0	0	0	0
Phen. Sulph. Phthal. (%)	50	25	51	49	39	33
Galac. Tol. Deviation (%)	−33	−83	±0	−25	±0	+25
Non-Protein Nitrogen (mgm.)	40	29	33	26	29	31
Uric Acid (mgm.)	4.4	2.3	4.4	3.3	3.8	3.7
Sugar (mgm.)	100	77	82	83	81	71
Haemoglobin (%)	95	65	85	95	100	70
Erythrocytes (10^6)	4.93	3.34	4.14	4.81	4.97	4.33
Leucocytes (10^3)	5.40	11.9	4.9	6.95	9.60	5.30
Neutrophiles (%)	54	66	45	52	50	62
Lymphocytes (%)	35	27	46	40	38	25
Eosinophiles (%)	6	2	4	1	2	5
Monocytes (%)	5	5	5	7	9	3
(Basophiles) (%)	—	—	—	—	1	5

THYROID FAILURE WITH GALL BLADDER COMPLICATION

GROUP I

Case B-480. The patient's chief complaint was of abdominal pain coupled with jaundice. The latter condition was first remarked eighteen months previously and the first attack lasted for about a month, with characteristic stool and urine findings. The jaundice cleared up under medication. Following this, there was a period during which she became very fatiguable and mentally sluggish, with occasional attacks of acute nervous instability. Nearly 20 years before she had been treated for myxedema and from time to time in the interim had had occasional courses of thyroid medication.

Family History: Father and one sister died with symptoms similar to those of the patient.

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*See discussion of case.

Past History: She reported only measles at the age of 26, severe pneumonia followed by abscess in the right lung at 43, an injury to the spine at 37 which caused temporary paralysis of the left leg. She matured at the age of 9 and had apparently passed through the menopause a few months before admittance. The menstrual history was normal except for menorrhagia prior to the cessation of the periods. She had been married twice, her first experience lasted 3½ years, with three pregnancies, resulting in one surviving child, a miscarriage at three and a half months, and a child who died at birth. Her second marriage produced one miscarriage four years previously, resulting from a fall while three months pregnant. She had always been constipated; had had a tendency to obesity at times, checked by drastic dietary.

Physical Examination: The patient was deeply jaundiced, obese woman, 52 years of age, apparently asthenic and showing a marked mental sluggishness. The scleræ were deeply jaundiced, the few remaining teeth were in poor condition, tonsils were enlarged and cryptic, and there was a slight thyroid enlargement. There was a tenderness on palpation over the entire abdomen, more pronounced over the liver, which was somewhat enlarged; the pubic hair was scanty, skin coarse, dry and deeply pigmented, and large fat deposits were observed on the breast and abdomen. The abdominal reflexes were reported as absent.

Laboratory Summary: The patient was 45 per cent above her predicted weight, while the lung volume was less than half that of prediction. She had a basal rate of —36 per cent, with marked bradycardia and substantially normal blood pressure. The urine showed albumin and bile, also a positive "urobilinogen" test. Phthalein elimination was but 25 per cent. The patient's sugar tolerance was greatly lowered. Blood sugar was slightly below normal. Her blood showed a definite secondary anæmia, a slight leucocytosis, and a substantially normal formula.

Pelvic Examination showed residua of early child-bearing; a large fundus was freely movable and in good position; the findings were otherwise normal.

The sella by *radiography* was normal; the lower teeth showed absorption.

Eye Examination showed contraction of the form and color fields too marked to permit the delineation of the blind spots.*

Neurological Examination disclosed evidence of multiple neuritis and emotional instability.

Laryngological Examination showed hypertrophied and infected tonsils.

An earlier gastro-intestinal radiographic study had demonstrated a cholecystitis.

Diagnosis: The patient's condition was obviously thyroid failure coupled with gall bladder disease and a probable dysfunction of the liver. There was also a definite psychoneurosis.

Comment: Operation for the gall bladder condition was recommended, to be accompanied and followed by controlled thyroid medication. The operation was successful, a grossly diseased gall bladder being removed. Her jaundice cleared rapidly and she was discharged to continue her thyroid medication. Some two years later she returned to the clinic in a much improved condition. Her thyroid medication had been somewhat intermittent and she had increased in weight to 68 per cent above prediction. A duodenal study showed considerable disturbance of biliary function of the liver, a residuum of the earlier gall bladder condition. Her earlier low sugar tolerance had increased to the normal. The eye grounds were still further contracted. Under controlled thyroid medication for a few weeks her basal rate was brought promptly to a normal level. The nervous instability of which she had earlier complained had returned, but a number of social factors had appeared which were undoubtedly of definite significance in producing this result. In spite of this, the mental picture was greatly improved.

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*Fields of this type have been recorded by one of us in a number of cases of gall bladder and liver disease. Unpublished data, A. W. R.

CASE B-467. The patient's chief complaint was of "bilious attacks," from which he had suffered since childhood. They were characterized by constipation, acid eructation, drowsiness, and dull headaches following meals. There was also a mental dullness of which the patient was acutely conscious, and periods of mental depression. He had attempted to correct the condition by dieting and had eliminated a number of articles of food which he believed to be badly tolerated. Investigation showed that his remaining dietary regimen was entirely inadequate, although containing a maintenance quantity of protein. There has been a gradual loss of weight and a general physical depression.

Family History: The father was reported as having had a liver trouble of unknown character and possibly exophthalmic goiter.

Past History: The patient was born in South Africa and lived there until the age of 19. He had lived in England since that time, except for two years in the army in France and in the Salonika campaign. He reported most of the minor ailments of childhood, malaria in 1916 with jaundice, and several brief recurrences of this condition until an attack of rheumatic fever in 1917. He had had no malaria since this latter condition, but had had two attacks of jaundice in 1925. He had been subject to asthma since the age of 9, also bronchitis; he had an attack of influenza at the time of the epidemic. He reported a possible protein sensitivity to horse dandruff and to feathers. His appetite was good, but digestion was poor. Among other interdicted articles of food were eggs, cheese, and fats of all kinds. He had used Epsom salts and calomel very freely.

Physical Examination showed a very well set up and athletic. but undernourished, Englishman of 31 years of age. There was a yellowish tinge to the skin and the conjunctivæ were yellowish. His abundant black hair was tinged with gray; the teeth showed much dentistry; there was some minor adenopathy in the neck. The heart was normal and there was no tenderness over the gall bladder. The left testicle was undescended. The thyroid was not enlarged. The remaining findings were substantially normal.

Laboratory Summary: The patient was 25 per cent under his predicted weight, showed a basal rate of —29 per cent, with low blood pressure, bradycardia, and somewhat subnormal temperature. The scanty urine was free from abnormalities except a high residual nitrogen. The sugar tolerance was somewhat depressed. The blood chemistry gave evidence of some retention. The blood morphology showed a lymphoid blood with a slight eosinophilia, undoubtedly due to his protein sensitivity.

Repeated examination of the blood for plasmodia failed to show them.

Neurological findings were normal.

Abdominal findings were normal.

Endermal Tests: A positive response to egg and doubtful positive to wheat and milk was found; the reaction was negative to a large number of other proteins.

Radiography: A gastro-intestinal series was substantially normal. The skull and sinuses were normal. The chest showed increased density at the right apex, with haziness and scattered mottling over the whole lung area. A Graham test by the oral route was negative.

Duodenal Function Test (McClure): The patient showed a very marked disturbance of biliary function.

Audiogram: Substantially normal hearing was found.

Stool Examination: Blood, ova, parasites, and cysts were reported absent.

Cardiac Examination: Beyond a short systolic murmur, with the first sound at the apex, a frequent finding in normal individuals, the findings were entirely normal.

Eye Examination: Gave normal findings.

Discussion: On the basis of the findings given, a diagnosis of hypothyroidism, coupled with a liver dysfunction, was established. Thyroid medication was suggested for the first, and duodenal lavage for the second. Under this treatment the patient's condition rapidly cleared; he gained in weight, the jaundice disappeared, sugar tolerance became normal, and the general laboratory picture showed marked improvement, including a disappearance of the blood chemistry findings suggesting lowered kidney permeability (see pseudonephritis later). Shortly after this study the patient returned to England, and we are advised that he has had one or two relapses of the liver condition, which, however, have yielded to further treatment by lavage.

Case B-845. The patient's chief complaint was of skin eruption and an inability to digest certain foods. In 1909 he developed a skin disease diagnosed as ichthyosis. The skin became hypertrophic; there was much exfoliation, with a transitory and recurrent erythema. The latter seemed to depend primarily on the use of such foods as fat, fruit, and milk. Milk caused abdominal pain, while fats have produced a yellow color of the skin. High protein diet will also cause the yellow color, but the patient could take liver freely, an interesting point in view of his fat intolerance.

Family History: Two grandparents died of cancer, and the mother had been operated upon for gall stones.

Past History: The patient reported the minor ailments of childhood, together with pneumonia and diphtheria in early years. Influenza at the time of the epidemic was complicated by an involvement of the antra and ethmoids, which later disappeared without treatment. An appendectomy was performed in 1909, and an exploratory laparotomy in 1917 showed an alleged normal gall bladder. The patient had also been operated upon for tonsilitis, hemorrhoids, and had had several infected teeth extracted. He complained of an occasional unilateral headache, marked optic fatigue, occasional pain in the right ear, and recurrent pharyngitis after the use of milk or cream. Recently he had had attacks of precordial pain, which was aggravated by the use of thyroid. Tingling and numbness of the hands and feet and some myalgia had been recent developments. For some time past he had had a non-specific prostatitis. He had lost 17 pounds in the six months prior to his admission.

Physical Examination: The patient was a well-developed but distinctly emaciated white man, 37 years of age; the face was pallid with a definite lemon-yellow cast; the conjunctivæ were slightly yellowish. There was a moderate deviation of the septum. No thyroid enlargement was present. The heart sounds were indistinct, the beat irregular, with recurrence of several rapid beats which were not typical extrasystoles. There was definite bradycardia and hypotensive blood pressure. The right testicle was somewhat tender and there was possibly tenderness over the gall bladder. Minor inguinal and definite cervical adenopathy was found. The skin was dry, scaly, and hypertrophic. The tendon reflexes were reported as sluggish.

Laboratory Summary: The patient was 33 per cent below his predicted weight, the lung volume but slightly below prediction. The basal rate was —33 per cent. The blood pressure recorded at this time was distinctly higher than upon several other observations, but still hypotensive. There was bradycardia. The sugar tolerance was normal; the blood uric acid high. There was a slight secondary anæmia and borderline leukopenia. The blood was lymphoid in type, with a slight relative increase in the eosinophiles.

Skin Examination: There was a mild ichthyosis, suggestive of thyroid failure. Several other possibilities were considered and rejected on the ground of other observations.

Endermal Tests: The patient reacted positively to several cereals —celery, spinach and peas—and negatively to a large number of common food proteins.

Cardiac Examination gave entirely normal findings. The cardiogram showed a slurring of the QRS complex and the contour of the "T" wave in leads II and III was suggestive of possible myocardial impairment, without defining it.

Neurological Examination gave substantially normal findings, except for a possible loss in deep sensation over the lower extremities and somewhat diminished reflexes.

Abdominal Examination disclosed no abnormalities, failing to confirm the earlier report of tenderness over the gall bladder.

Eye Examination showed normal conditions.

Radiography of heart, lungs, diaphragm, lumbar spine, hips, pelvis, and skull disclosed no abnormalities.

Neutral Red Test: Normal.

Gastric Examination: Abundant free hydrochloric acid.

Endoscopic Examination showed an enlarged, tender prostate, with involved left seminal vessels and normal bladder.

Duodenal Function Test showed marked hepatic disturbance.

Icteric Index: 50-75.

Van den Bergh: Negative.

Pancreatic Enzyme Examination showed normal concentration and activity.

Laryngological Examination gave normal findings.

Microscopic Examination: Numerous giardia were demonstrated in the duodenal contents.

Discussion: The case presented a number of interesting possibilities. Primary anæmia was ruled out by the tests given above and by repeated examinations of the blood, none of which gave any indication of this condition. The normal pancreatic lipase content referred the patient's fat intolerance to the biliary disturbance. The demonstration of the giardias in the duodenal contents (a fact of which the patient had been earlier advised) offered a basis for the patent disturbance of gall bladder and presumptively liver function. In addition there was a definite thyroid failure. It was felt in this case that the invasion of the duodenum by the parasite was probably a starting point for the general condition. Duodenal lavage with substances such as magnesium sulphate, known to be antagonistic to these parasites, was advised. Thyroid medication was also recommended, recognizing, on the basis of past experience that complete correction could be expected only when the parasites had been exterminated and the liver brought back to a normal level of functional activity. Later advices showed some improvement in the condition, but the giardia are still present.

GROUP II. PSYCHOSES

CASE B-35. The patient's chief complaint was easy fatigability, with lameness in the left knee and general nervousness. The entire picture was dated from the birth of the patient's last child in 1918, five years before the patient was seen. Several earlier medical contacts had ascribed the patient's condition to pelvic disorders and an operation had been advised, which had been refused, however. The patient was in a markedly depressed condition, from which she would emerge into sudden bursts of temper without exciting cause. There were several halucinations, the whole defining a manic depressive psychosis.

Family History was not significant.

Past History: The patient reported the minor ailments, scarlet fever and pneumonia in childhood and typhoid fever at the age of 26. A tonsillectomy had been done the year before. She had been subject to head-colds. Her bowels were constipated. Otherwise the history was not remarkable. She had been married for 12 years and had borne three children without miscarriage. The menstrual history was not remarkable beyond brief and somewhat scanty periods.

Physical Examination: The patient was a well-developed, somewhat obese white woman, 41 years of age. The skin was very dry and scaly, hypertrophic, and did not pit on pressure. The hair of the head and eyebrows was coarse and somewhat scanty. The palpebral fissures were narrow, the upper and lower eyelids were puffy, the tongue increased in size, but without tremor on extension and not prominently fissured. A few bubbling rales were reported in the region of the bronchi; blood pressure was low, and there was definite bradycardia; the hands were broad, fingers short, the nails were thickened and striated; the facies was typical of myxedema. The patient's mental reaction was very sluggish and the speech thick, possibly as the result of enlarged tongue.

Laboratory Summary: The patient was overweight and nearly 50 per cent below predicted lung volume. The basal rate was —50 per cent, the blood pressure low, the pulse normally very slow, though at the time of the reported basal examination it was 71. There was a marked subnormal temperature. The low alveolar carbon dioxide was probably due to the patient's inability to cooperate. The sugar tolerance was slightly increased. Blood sugar was low, and the blood morphology showed a secondary anæmia with a 5 per cent basophilia. An interesting point in connection with this case is recorded in a basal test done during the latter part of the patient's stay. At this time she had developed a slight infection and showed a temperature of 100.8° F. The basal rate at this time was —25 per cent. If we calculated to her usual daily temperature this would correspond to a value around —60 per cent. Another interesting point was found in a series of comparative blood pressure measurements. The first recorded, at a time when the patient was in a tense, nervous condition, was 166/110. Subsequent measurements made under quiet conditions showed an average slightly below that recorded in the table.

Eye Examination: The patient showed substantially normal findings, except for slightly enlarged blind spots and cutting of the upper form fields, due to lid droop.

X-Ray: Chest and skull were normal.

Pelvic Examination gave normal findings.

Neurological Examination: There was no evidence of organic nervous lesion. The patient's mental state was ascribed to her glandular condition.

Discussion: The presenting data warranted the diagnosis of marked hypothyroidism with myxedema. Thyroid medication was recommended, and this was actively carried out. In the course of a few months the patient showed the usual remarkable results which may be confidently expected from controlled thyroid medication in an uncomplicated case of thyroid failure. A most interesting feature of the case was the complete disappearance of the mental symptoms, which at the end of five years have shown no tendency to return.

CASE B-528. The patient's chief complaint was of a recurrent profound mental depression, of which this was the latest attack, the first having appeared some 23 years before. Three years later there was a recurrence which cleared up spontaneously in a few months, and again 14 years later there was a three months' attack. In the preceding year there had been a downward tendency, but the progress had been so slow that it did not become serious until a short time before admission. The last attack had been characterized by an attempt at suicide, the earlier seizures having shown no tendency toward self-destruction.

Family History: Beyond a sister with epilepsy, the history was not informative.

Past History: The patient reported the usual minor ailments with freedom from any serious disease. He had a slight productive cough apparently arising in a throat irritation. The bowels were regular. There was a question of jaundice many years before. He had been overweight for a number of years.

Physical Examination: The patient was a well-developed, obese man of 61 in a state of marked mental depression. His complexion was ruddy, his skin was normal in texture and moisture, the breath was foul. Several teeth were missing and the remainder in only fair condition. The heart and lungs were apparently normal; the abdomen obese and not tender on palpation; the knee jerks were not elicited.

Laboratory Summary: The patient was 26 per cent overweight; he showed a basal rate of —29 per cent; the urine volume somewhat low; the urine contained a trace of sugar. The protein intake was below a maintenance level; the residual nitrogen high. Sugar tolerance was normal. Blood morphology showed a lymphoid type.

Radiography: The sella was small; teeth were normal.

Cardiogram: Normal.

Neurological Examination gave no evidence of organic nerve lesion.

Eye Examination disclosed slight irregularity of pupils with yellowish discs and some cutting of the upper form fields due to lip droop.

Psychiatric Examination defined a manic depressive psychosis in the depressed phase.

Discussion: Beyond the trace of sugar in the urine, which is occasionally observed in uncomplicated mental cases, and which in the present instance is balanced by the normal galactose tolerance, the presenting picture is one of hypothyroidism. Another possible explanation of the sugar anomaly might lie in the record of an earlier jaundice, but this was so many years ago as probably to be devoid of meaning. Thyroid medication was advised and given with apparently complete recovery on the part of the patient. There has been no subsequent evidence of recurrence in the years that have supervened. Too much weight should not be laid on the correction of the mental condition, but it is interesting to note that the normalizing of the physical state coincided with that of the mental. It may, however, be no more than a coincident remission.

Case B-875. The patient's chief complaint was fatigability. She had suffered from a manic depressive psychosis for a number of years. Her childhood home conditions were unhappy but she evidenced no marked depression until 10 years ago when she divorced her first husband after one year of married life. For the next two years she showed periods of depression in the fall and winter, followed by terms of exaltation in the remaining two seasons. She attempted suicide in 1919 but voluntarily gave up her attempt out of consideration for her family. She was married again 2 years later, an event which involved a marked change of residence. Has had recurrent periods of depression, during one of which she again attempted suicide. She had received a variety of endocrine therapy without result. Her second attempt at suicide followed a three weeks' course of thyroid medication.

Family History: Her maternal grandfather committed suicide. The history is otherwise irrelevant.

Past History: She had minor ailments, diphtheria and scarlet fever in childhood, jaundice at the age of 7, frequent attacks of tonsilitis and quinsy sore-throat until a tonsil and adenoid operation at the age of 10, which was repeated 12 years later. She has occasional headaches, some tinnitus, and is usually constipated. Her menstrual history shows early onset, marked irregularity, and normal periods. A few years previously she was markedly obese and is still much overweight. She usually loses weight during depressed periods. She has had no children by either marriage.

Physical Examination: The patient is a well-developed, obese woman 32 years of age. The hair is fine and abundant and of normal distribution; there is some nasal obstruction; the thyroid is not enlarged; the heart and lungs are normal; she has somewhat low pulse and blood pressure; the remaining findings are normal.

Laboratory Summary: The patient is distinctly overweight. Her basal rate is -32 per cent, blood pressure and pulse somewhat low. There is a slight oliguria, somewhat high residual nitrogen, inadequate protein intake, and slightly low phthalein output. The sugar tolerance is slightly depressed. Blood sugar is a low normal. The blood is lymphoid in type.

Pelvic Examination: Normal.

Orthopedic Examination: The patient shows poor posture; otherwise is substantially normal.

Radiography shows prominent clinoids, but no other abnormalities.

Cardiogram: Normal.

Eye Examination shows yellowish discs, slightly enlarged blind spots.

TABLE XVIII

	Thin Without Myxedema		Sterility		Deafness	
Case Number	B-44	S-235	S-1013	S-1528	S-407	S-1466
Diagnosis	—	—	—	—	—	±
Sex	F	F	F	M	M	F
Age (yrs.)	41	49	26	34	40	19
Height (cm.)	170	167	160	178	163.5	161.5
Weight (kgm.)	47.8	66.0	83.2	80.9	60.2	63.0
Weight Deviation (%)	−29	−8	+34	+11	+18	±0
Lung Volume Deviation (%)	+6	−32	−12	−3	−6	−10
Basal Rate Deviation (%)	−32	−34	−26	−26	−22	*−12
Blood Pressure (mm.)	108/90	105/58	102/64	106/68	132/80	110/70
Pulse Rate (per min.)	64	54	52	56	72	76
Temperature (deg. F.)	97.6	97.2	97.8	97.1	98.9	98.0
Alveolar CO_2 (mm.)	34	34	43	39	38	43
Urine Volume (cc.)	1420	1280	940	1350	1510	760
Spec. Grav.	1.013	1.019	1.025	1.023	1.015	1.029
Albumin	0	0	0	0	0	0
Casts	0	0	0	0	0	0
Sugar	0	0	+?	0	0	0
Total Nitrogen (gms.)	8.68	10.79	10.70	12.00	9.63	10.94
Residual Nitrogen (%)	5.4	20.4	11.8	10.0	13.6	11.5
"Urobilinogen"	0	0	0	0	0	0
Phen. Sulph. Phthal. (%)	51	35	58	69	45	35
Galac. Tol. Deviation (%)	±0	±0	—	±0	—	−25
Non-Protein Nitrogen (mgm.)	42	29	32	30	25	32
Uric Acid (mgm.)	3.8	2.7	2.8	3.6	3.2	3.0
Sugar (mgm.)	87	105	100	96	100	93
Haemoglobin (%)	85	95	85	100	90	90
Erythrocytes (10^6)	4.36	4.86	4.37	4.95	5.46	5.36
Leucocytes (10^3)	6.80	5.70	7.80	5.20	8.20	8.50
Neutrophiles (%)	39	41	61	50	61	60
Lymphocytes (%)	55	50	36	41	34	28
Eosinophiles (%)	2	3	1	2	0	0
Monocytes (%)	2	5	2	7	5	10
Basophiles (%)	2	1	—	—	0	2

*Transition level.

Psychiatric Examination confirms the diagnosis of a manic depressive psychosis, in the depressed phase.

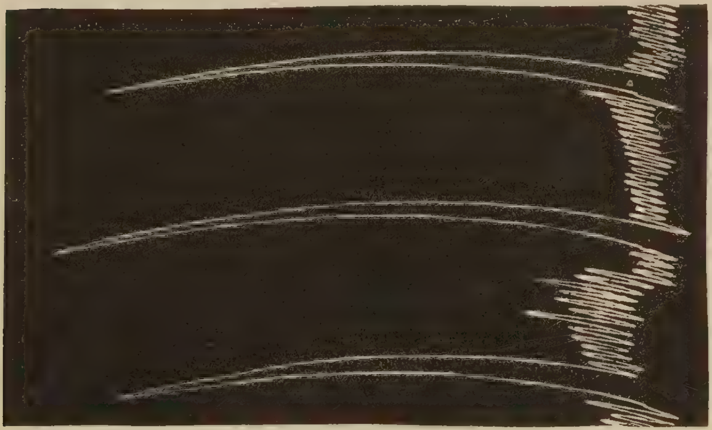
Discussion: Again barring the slightly lowered sugar tolerance, the picture is one of uncomplicated thyroid failure. The patient's history of an earlier attack of jaundice might offer a possible explanation of the sugar anomaly or, as noted above, it may be intrinsic in the mental condition, as we have observed it in a number of such cases which offered no other explanation for the abnormality. This case is still under treatment and the outcome has not been determined.

GROUP III. AMYXEDEMIC THYROID FAILURE

CASE B-44. The patient's chief complaint was of very severe headaches from which she had suffered since childhood. She usually woke up with them in the early morning. They were completely prostrating, lasted about a day, might come at regular intervals of two or three weeks and again she might be free for two or three months. They were not accompanied by disturbances of vision, but she was often nauseated. A mild glycosuria had been observed on several occasions and the patient found that the headaches were less severe and frequent when under a dietary modification which rendered her sugar free.

Family History: Both the father and one sister had similar headaches.

PLATE 1



Past History: She reported the minor ailments of childhood, one attack of jaundice, severe tonsillitis, and several accidents not relevant to the present difficulty. She had been underweight for a long time. She developed transitory arthritis with urticaria after a serum injection a year previously. She complained of dyspnoea, of palpitation, and occasionally precordial pain. The respiration rate showed a peculiar anomaly with a deep sighing breath at fairly regular intervals. (See Plate I.) The patient was conscious of this and found it extremely embarrassing. The menstrual history shows a normal onset, regularity with a shortened interval and somewhat profuse flow. She had had intermittent attacks of urinary frequency.

Physical Examination: The patient was a poorly developed and nourished woman 41 years of age, with skin smooth and moist, thyroid not enlarged, breasts atrophic, heart and lungs negative, hypotensive blood pressure. The routine neurological examination disclosed only exaggerated knee jerks.

Laboratory Summary: The patient was much below her predicted weight. The basal rate was —32 per cent with low blood pressure, somewhat slow pulse and slightly sub-normal temperature. The basal rate as recorded was undoubtedly too high as the patient was slightly restless. That recorded is the lowest of several observations, all of which, however, were below —20 per cent. Alveolar CO_2 was slightly low but this was probably due to an inability to exhale properly. The urine was normal; nitrogen partition, normal; phthalein test a low borderline normal; sugar tolerance was normal. The blood nitrogen was slightly high; the morphology showed a slight secondary anemia and a lymphoid blood. A provocative urea curve was somewhat low, offering another evidence of lowered kidney permeability.

Barany Test: Normal.

Discussion: While the patient violated most of the conventional clinical signs of hypothyroidism, the essential features of the laboratory picture could be interpreted only in terms of thyroid failure. She was placed on thyroid extract and in a short time showed a complete clinical cure. Her only relapse of significance during the past 5 years was on one occasion when she went for a number of weeks without medication. Resumption of her medicine produced an immediate correction. A short time after treatment was started a brief check-up examination was made. The patient had gained considerably in weight (this is a constant finding in this type of thyroid failure, the patients being initially underweight). The blood pressure had increased to 120/80, the temperature to 98.6°. the basal rate was normal. The phthalein output showed a definite increase. Non-protein nitrogen of the blood had fallen to 30 mgm., while the uric acid had fallen off a few tenths. All the earlier evidences of lowered kidney permeability had practically disappeared. The blood morphology had improved. the lymphocytes having fallen to 37 per cent. This was one of the early cases of what we have designated a "pseudonephritis," on which comment has been made earlier in the paper.

CASE S-235. The patient's chief complaint was of fatigability which apparently began in childhood. At the age of 11 she began to put on weight. localized chiefly in the legs. This condition had been a serious annoyance and she had made numerous efforts to correct it but without success. The patient had a wide variety of medical contacts, and had been under intermittent glandular therapy with pituitary extract predominating. Four years before she had developed urinary frequency which was ascribed to cystitis. Two years prior to admission she had had an intestinal stasis demonstrated by the radiography. A radical diet with some glandular therapy had produced some subjective improvement. The bowels were markedly sluggish. There was a loss of hair and dry, rough skin. An inhibiting feature was a feeling of mental depression which the patient was not able to combat.

Family History: Was irrelevant except for the fact that her relatives were all tall, large people.

Past History: She was never strong. She had the usual children's diseases; frequent sore-throats: from 7 until 15 much trouble with running ears. During her school years she found it difficult to concentrate. A tonsillectomy at 30 produced some benefit in the general condition. The catamenial and marital history were negative.

Physical Examination: The patient was a fairly developed, poorly nourished woman of 49. The hair was dry and short, the skin dry and rough, the thyroid was not palpable, the blood pressure was hypotensive. The legs were disproportionately large but not edematous. The remaining findings were substantially normal.

Laboratory Summary: The patient was 8 per cent underweight, and definitely below predicted lung volume. The basal rate was —34 per cent, with low blood pressure, bradycardia, and sub-normal temperature. The urine was normal except for a very high residual nitrogen. The phthalein output was definitely below normal. The low alveolar CO_2 was probably apparent rather than real. The sugar tolerance was normal. The blood showed a marked lymphocytosis.

Neurological Examination showed no abnormalities.

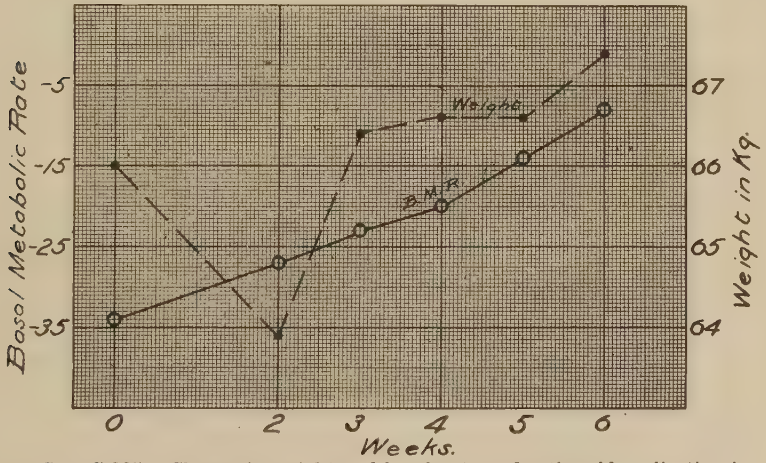
Barany Test: Normal.

Eye Examination showed slightly enlarged blind spots.

Radiography showed a normal sella.

Discussion: That the patient presented an endocrine disorder was patent from the facts as obtained. Further, a thyroid failure was the only endocrinopathy in harmony with the data. Thyroid medication was advised, and through the complete cooperation of the patient it was possible to check the progress of the case over a period of six weeks. Certain significant results are given in the accompanying graph. (See Plate II.)

PLATE II



Case S-235. Change in weight and basal rate under thyroid medication in a case of failure.

It will be noted that there was a loss of weight during the first two-week period which promptly recovered, and the patient showed a net gain of 1.4 kgm. in the six weeks' interval. Later observation had shown a re-distribution of weight, the obesity of the legs having become definitely less.

GROUP IV. STERILITY.

CASE S-1013. The patient's chief complaint was of sterility, coupled with dysmenorrhea. She had been married for two years without becoming pregnant and without at any time having practiced contraception. She matured at 11, and the history gave regular periods of somewhat brief duration with scanty flow. There had always been pain, appearing shortly after the flow began and lasting about two days. Numerous clots were passed. She had tried various forms of medication, including ovarian extract, without betterment.

Family History: Several cases of malignant neoplasm were recorded; the remaining history was irrelevant.

Past History: The patient reported only measles and whooping cough of the minor ailments and none of the more severe conditions. There was a history at the age of 6 of a fall with trauma to the head, which left no apparent after-effects. Two curettage operations had been performed and fifteen months before her hospital entry one fallopian tube had been taken out. The remaining history shows some intermittent gastro-intestinal disturbances, constipation, and a gain of some 20 lbs. within the past two years. She began to become obese at the time of the onset of the catamenia but had been able to control it in some measure by diet.

Physical Examination: The patient was a well-developed woman, 26 years old, exhibiting a generally distributed obesity. There was a symmetrical thyroid enlargement of moderate amount, a slight tenderness over McBurney's point, and certain postural defects, probably ascribable to obesity. The findings were otherwise normal.

Laboratory Summary: The patient was 34 per cent above her predicted weight. The basal rate, under fairly satisfactory conditions, was 26 per cent below prediction, the lung volume was but slightly impaired, the blood pressure was low with bradycardia. The urine volume was somewhat low with a questionable positive test for sugar. The residual nitrogen fraction was distinctly above the normal; the blood was lymphoid in type.

Radiography showed a normal skull.

Pelvic Examination gave no evidence of pathology.

Discussion: The picture defined by the laboratory tests was considered to be fairly typical. A diagnosis of thyroid failure was offered and thyroid medication instituted. A subsequent report from the patient's physician was to the effect that shortly after beginning treatment the patient had conceived and borne a normal child.

CASE S-1528. This case is particularly interesting. It is one of the series of sterility studies which the authors and their colleagues have been conducting for some time. The work in general will be described elsewhere in the near future. It is enough to say here that it involves a very thorough study of both partners to the marriage, one phase of which deals with possible endocrine factors.

The patient's chief complaint was the sterility of his marriage, as in the course of three years his wife had failed to conceive. The patient himself was somewhat asthenic and had been so for something over a year. The removal of an abscessed tooth during this period produced only a slight temporary relief from this symptom.

Family History was not significant.

Past History: The patient reported the minor ailments of childhood, scarlet fever, lobar pneumonia, and a questionable attack of small-pox in childhood. He had a mild attack of influenza at the time of the epidemic. There had been a moderate loss of hair. He was both astigmatic and myopic and showed a susceptibility to rhinitis. He complained of coldness of the extremities and reported some dermographia.

Physical Examination showed a well nourished, slightly obese white male, 34 years of age. The hair was thin, and there was a partial alopecia. The remaining examination gave substantially normal findings.

Laboratory Summary: The patient was slightly above predicted weight, had a normal lung capacity and a basal rate of —26 per cent with low blood pressure, slow pulse, and a slightly sub-normal temperature. The urine was normal except for a high residual fraction in the nitrogen partition. The sugar tolerance was normal; the blood, lymphoid in type. In the sterility study the wife was eliminated as a contributing factor.

Genitourinary Study: No physical abnormalities were found, while the condom specimen was normal in regard to the number, motility, and morphology of the spermatozoa. A post-coital examination showed the presence of spermatozoa, about half of which were dead or non-motile.

Cardiogram: Normal.

Discussion: The laboratory examination demonstrated a clear-cut thyroid failure in the husband. The chief interesting feature lies in the fact that on the basis of the condom specimen the husband would have been eliminated as a factor in the sterility equation under the ordinary conditions of practice. The patient was placed on thyroid medication, the wife conceived inside of two months, and after an uneventful pregnancy was delivered of a normal child.

GROUP V. DEAFNESS.

CASE S-407. The patient's chief complaint was of a progressive deafness which had lowered his aural acuity in the left ear so that only loud noises could be apprehended. In the right ear the hearing was poor but the impairment less pronounced. The condition began at the age of 30 involving first the left ear only. He had been troubled with tinnitus.

Family History: The mother suffered from the same complaint. The remaining family history was irrelevant, except for one aunt who was insane.

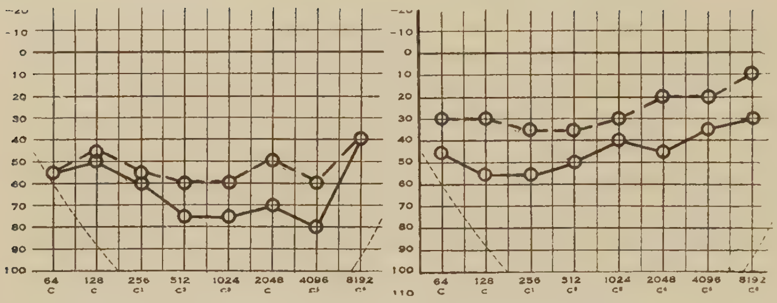
Past History: The patient had the usual childhood ailments but had been perfectly well during his adult years.

Physical Examination: The patient was a well-developed male of 40 with an obesity of general distribution; the muscles were flabby, and the mental reaction sluggish. Both ears exhibited deafness which in the left was more pronounced. The remaining findings were normal.

Laboratory Summary: The patient was overweight. His basal rate of —22 per cent derived from a not altogether satisfactory test. The true rate was probably somewhat lower. There was a high residual nitrogen in the urine and a slight relative lymphocytosis.

Audiogram (see Plate) showed marked loss of hearing in both ears, more pronounced in the left.

PLATE III



Left

Right

Case S-407. Audiograms showing improvement after 6 months of thyroid medication.

Discussion: It was not possible to make as thorough a study on this case as was desired, but a tentative diagnosis of thyroid failure was offered as being the most probable condition. The patient responded well to thyroid medication, and six months later there had been a definite improvement in hearing, as shown by the second audiogram curves (see Plate).

CASE S-1466. The patient's chief complaint was of deafness in the right ear which had begun about a year before without any apparent cause. It had been progressive, although at the time of the examination it was felt to be at a standstill. She experienced tinnitus and exhibited paracusis.

Family History: There was a marked history of cancer on the paternal side.

Past History: The patient recorded minor ailments, an attack of influenza during the epidemic, followed by arthritis, for which she was under treatment. Four years previously she had been operated on for a felon and in the preceding October an appendectomy had been performed. She complained of dyspnoea, some palpitation, and intermittent constipation. Her menstrual history was not remarkable. For some time the patient had been very fatigable. She had gained slightly in weight. With somewhat unusual self-perspective she stated that she had become very irritable.

Physical Examination: The patient was a well-developed, well-nourished girl of 19. During the examination there was a constant slight movement of hands and feet, occasionally of the body and extremities. The eyes were normal; there was no tremor of the tongue; the thyroid was slightly enlarged. She exhibited some tenderness near the appendectomy scar. There was no tremor of the hands but the fingernails were bitten off. The skin was dry and on the legs showed fine scaling.

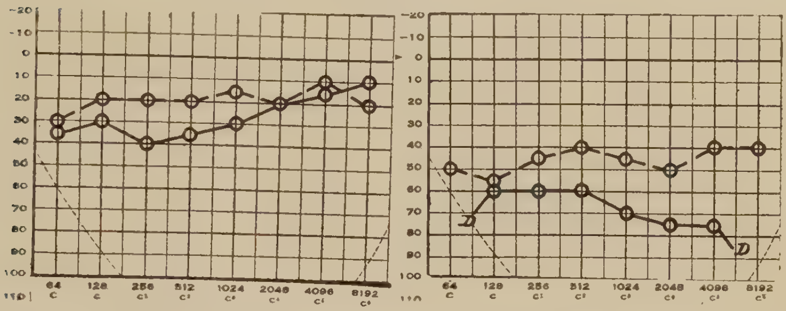
Laboratory Summary: The patient's weight agreed with prediction. The basal rate was —12 per cent, under fairly satisfactory conditions (v. s.). The blood pressure was somewhat low, the urine small in volume, concentrated and containing an abnormally high residual nitrogen fraction. The sugar tolerance was slightly depressed. Blood chemistry and morphology were normal.

Neurological Examination: No evidence of organic nervous disorder was found.

Pelvic Examination gave normal findings.
Cardiogram: Normal.

Audiogram (see Plate) showed marked loss of hearing in the right ear and some loss in the left.

PLATE IV



Left

Right

Case S-1466. Audiograms showing improvement after 8 months of thyroid medication.

Discussion: The patient seemingly presented a thyroid dysfunction, not impossibly of the transition type. The basal rate of —12 per cent was felt to be certainly above the truth, and the cautious exhibition of thyroid medication was recommended. Eight months later the patient returned for a test of the aural acuity, and the audiogram (see Plate) showed some improvement in the left ear and marked betterment in the right.

TABLE XIX

	Familial Influence			
Case Number	S-1371	S-1456	S-1520	S-1438
Sex	M	M	F	M
Age (yrs.)	54	19	18	15
Height (cm.)	170	182.5	166.5	171.6
Weight (kgm.)	57.5	60.5	53.2	56.8
Weight Deviation (%)	+1	−15	−12	−1
Lung Volume Deviation (%)	−13	−3	−9	+2
Basal Rate Deviation (%)	(−10)	−31	−30	−21
Blood Pressure (mm.)	138/86	108/64	102/70	108/66
Pulse Rate (per min.)	54	67	60	62
Temperature (deg. F.)	97.7	97.0	98.4	97.8
Alveolar CO_2 (mm.)	57	48	41	42
Urine Volume (cc.)	1510	1280	1250	560
Spec. Grav	1.015	1.024	1.015	1.026
Albumin	+	0	+	0
Casts	0	0	0	0
Sugar	0	0	0	+
Total Nitrogen (gms.)	9.70	11.91	7.38	7.20
Residual Nitrogen (%)	5.7	11.7	4.7	11.9
P. S. P. (2 hours) (%)	37	36	59	57
Galactose—Normal (gms.)	30	30	40	30
Observed (gms.)	30	not done	not done	not done
Deviation (%)	±0			
Blood—N. P. Nitrogen (mgm.)	32	30	30	27
Uric Acid (mgm.)	2.8	3.3	3.8	3.4
Sugar (mgm.)	87	87	96	87
Haemoglobin (%)	80	85	75	95
Erythrocytes (10^6)	4.00	5.59	4.29	4.93
Leucocytes (10^3)	5.00	5.20	9.05	5.00
Neutrophiles (%)	52	56	62	56
Lymphocytes (%)	42	38	35	35
Eosinophiles (%)	0	0	1	1
Monocytes (%)	5	5	2	7
Misc. (%)	1	1	0	1

GROUP VI. FAMILIAL INFLUENCE.

While it is a frequent record that there is a constitutional tendency in thyroid disease, the cases given in the table above show this rather strikingly. Each one of them taken alone probably defines a case of thyroid failure. No two of them are exactly alike in the general laboratory picture. The father was the first member of the family to be admitted to the clinic, his presenting difficulty being asthenia of comparatively brief duration. His history showed a susceptibility to infection which dated back to early childhood. He had always been constipated and had developed some minor paraesthesias. The physical findings were substantially normal. His basal rate as recorded was distinctly above the truth. The urea index was distinctly below the normal, and this coupled with his low phthalein output and the urine examination suggested a slight lowering of kidney permeability. Radiographic findings were normal, but a laryngological examination demonstrated infected tonsils. Other features of the examination can be seen in the table.

The oldest son was the tall, thin atypical "thyroid failure." Fatigability was his principal difficulty. He also had frontal headache, chronic catarrh, and an earlier acute sinusitis with some paraesthesias of the extremities. His remaining examination was not striking except for a history of jaundice some years before. The

TABLE XX

	Hyperthyroid			
	1	2	3	4
Case Number	B-953	S-1895	S-1188	S-1596
Diagnosis	+	+	+	+
Sex	F	F	F	F
Age (yrs.)	6	72	33	23
Height (cm.)	115.5	161.0	162.0	161.0
Weight (kgm.)	17.7	48.0	45.0	85.9
Weight Deviation (%)	−13	−18	−29	+35
Lung Volume Deviation (%)	−56	−39	−35	−22
Basal Rate Deviation (%)	+18(?)	+22	+44	+55
Blood Pressure (mm.)	120/55	170/82	122/50	136/58
Pulse Rate (per min.)	116	100	92	122
Temperature (deg. F.)	99.2	98.8	98.0	98.6
Alveolar CO_2 (mm.)	38	41	44	44
Urine Volume (cc.)	170	960	960	1400
Spec. Grav	1.026	1.014	1.023	1.014
Albumin	+	+	0	+
Casts	0	0	+	0
Sugar	0	+	+	0
Total Nitrogen (gms.)	2.03	3.74	8.91	6.60
Residual Nitrogen (%)	7.7	7.2	12.8	8.3
"Urobilinogen"	0	0	0	0
Phen. Sulph. Phthal. (%)	61	69	55	48
Galac. Tol. Deviation (%)	−50	—	—	—
Non-Protein Nitrogen (mgm.)	30	32	29	26
Uric Acid (mgm.)	3.3	3.0	2.7	2.6
Sugar (mgm.)	93	105	109	75
Haemoglobin (%)	95	80	90	88
Erythrocytes (10^6)	5.14	4.68	4.93	4.32
Leucocytes (10^3)	6.75	5.05	7.90	9.50
Neutrophiles (%)	42	70	53	68
Lymphocytes (%)	35	25	38	29
Eosinophiles (%)	10	1	1	1
Monocytes (%)	13	4	8	2
Misc (%)	0	0	0	0

1. Young child, exoph. goiter. B. M. slight; sugar, large change.
2. Incipient recurrence long after operation.
3. Prompt recurrence after operation.
4. Recurrent after operation with obesity.

physical findings were substantially normal. X-ray studies showed obstruction of the nasal fossae.

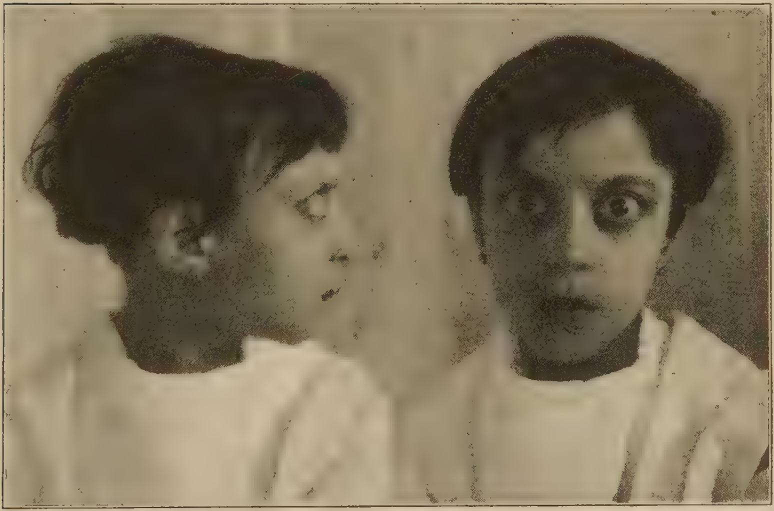
The second child, a daughter, is also an atypical "thyroid failure." The history as given is not suggestive and the physical findings were equally normal.

The youngest member of the family is perhaps less certainly hypothyroid. He did show a slight thyroid enlargement, the only one of the group giving any evidence of goiter. We were unable to study this case as thoroughly as desired and are by no means certain of the diagnosis. The slight glycosuria is a disturbing note, although several causes not incompatible with a thyroid failure could produce it. That he is "endocrine" is obvious. Further study would be necessary to fix with certainty the focus at fault.

GROUP VII. HYPERTHYROID.

The following group of cases have been selected as presenting certain possible interesting points in connection with a definite hyperthyroidism. The enormous general literature dealing with the condition renders it unnecessary to discuss cases falling in any of the conventional groups.

PLATE V



Case B-953

Case B-953. This little patient, a child of five, was referred to us with all of the outward evidences of well-marked exophthalmic goiter. The presenting complaint was her bulging eyes coupled with a marked nervousness. At about the age of a year and a half the mother noted that the child's eyes were beginning to bulge and that she was becoming nervous. The condition has been progressive, and because of her unusual appearance she has had difficulty with her schoolmates and had to be withdrawn shortly after entrance into her school. She had been under intermittent observation but without treatment.

Family History: The child is the oldest of three children, the other two being normal. The remaining history is not informative.

Past History: She was normally delivered, and breast fed for the first six months. She had measles at the age of four. The vision was not very good. She was subject to head colds and to sore-throats. She experienced no difficulty in breathing; the bowels were regular; there has been excessive perspiration on hands and feet and a skin eruption on the former.

Physical Examination: The patient was a well-developed but thin Italian child, 5 years of age, presenting a very marked exophthalmos, and moderate symmetrical thyroid enlargement. There were pulsations all along the anterior and lateral surfaces of the neck, and a well-developed bruit. The child showed lid lag and a positive Stellwag sign. The tonsils were large, cryptic and apparently infected. There was tachycardia and apparently some cardiac enlargement. The pulse pressure was very high. There was a slight fine tremor of the fingers, the knee jerks were equal and very active. The extensor test of the thigh suggested by Dr. Lahey was positive.

Laboratory Summary: The child was somewhat underweight and much below her predicted lung volume. A series of basal rate determinations gave a moderate increase above prediction. The standards for children of this age are not well defined and the value given represents a probable value from a series of different comparisons. There was tachycardia, a slightly febrile temperature, and a large pulse pressure, to which attention is again called. The urine was very scanty and contained albumin. The residual nitrogen fraction was normal. The sugar tolerance was half the normal level. The blood morphology showed a 10 per cent eosinophilia.

Radiography: There was no substernal enlargement; the heart was normal; the lungs showed mottling at both bases; the skull was normal; the optic canals were symmetrical and 4 mm. in diameter.

Skin Examination: This defined the eruption on the hands as punctate purpuric lesions of unknown etiology. In the examiner's opinion they were not associated with the exophthalmos.

Surgical Examination: "The thyroid was moderately enlarged. The exophthalmos was disproportionate to the apparent degree of toxemia."

Chest Examination: There was no evidence of present pulmonary disease. The cardiac enlargement was confirmed.

Neurological Examination: The findings were normal except for those characteristic of exophthalmic goiter.

Nose and Throat Examination: Cryptic tonsils of moderate size were found.

Cardiogram: This showed a normal mechanism with accelerated (125-135) rate. There was some evidence of possible auricular hypertrophy.

Eye Examination: The discs were yellowish and there was a thin retinal pigment with the choroidal vessels visible. The sclerae were bluish. The fields could not be obtained owing to the age of the patient.

Discussion: That the patient presented goiter with exophthalmos was obvious. Apparently, however, the toxicity of the gland was low insofar as the basal rate would be taken as an index. On the other hand the sugar tolerance was much depressed, and while some depression would be anticipated with an overactive thyroid, the relative degrees were disproportionate if the usual case be taken as a criterion. Suggestion of a congenital internal hydrocephalus was made by one of our associates, but x-ray examination of the skull gave no supporting evidence. As the child was not toxic to any marked degree she was discharged from the hospital without treatment with recommendation that she return within a few months for further study. In our experience primarily overactive thyroids at times undergo a spontaneous functional involution. Further, the extreme youth of the little patient seemed to warrant delay, since no evidence of marked toxicity was apparent. Two months later, however, the child having presented certain disturbing symptoms, she was referred to the Lahey Clinic for operation. We are much indebted to Dr. Robert L. Mason for the following information:

> "She was brought to the Deaconess Hospital on May 17. With her history you are, of course, familiar. On examination she presented a rather marked exophthalmos. The thyroid was uniformly enlarged and had the firm, elastic consistency of a hyperplastic gland. Her pulse rate was 132; weight was 40¾ pounds. The remainder of her general physical examination was essentially negative. Basal metabolism test the following morning showed a rate of +60. We believed the child to present a definite case of primary hyperthyroidism. She was placed on a pre-operative regime which included five minims of Lugol's solution three times a day, a high calorie diet, and rest in bed. On May 31st, her metabolism had dropped to +4; her pulse rate to 80, and she had gained 1¼ pounds. We thought her ready for operation.
>
> "On June 1st, operation was done. Four-fifths of a definite hyperplastic gland was resected. Pathological examination of the excised thyroid tissue showed it to be primary hyperplasia with moderate involution. There was a mild reaction following operation, which, however, had entirely subsided by seventy-two hours. Her subsequent course was satisfactory and uneventful. On discharge, she was doing very well. She was given a prescription of five drops of Lugol's solution taken each week for three months, at the end of which time she was to have a check-up for metabolism."

In the case of this child we are by no means certain that the obvious thyroid condition was not complicated by some other and extraneous effect. The preliminary study gave several possible evidences that this might be the case. She will be studied later in the hope that additional light can be thrown on the condition. It is quoted here, partly because of the somewhat unusual youth of the little patient and because it possibly illustrates the sugar anomaly of which note was made in the earlier section. In this connection we have had opportunity to make a more complete study of an adult woman in whom no complicating superimposed effect could be demonstrated. The significant data are given in the following table:

TABLE XXa

Date	Interval (Week)	Blood Pressure	Pulse	Basal Rate	Weight	Sugar Tolerance	
Dec. 6, 1926	0	132/54	84	+6	52.2		
Dec. 13, 1926	1	118/50	86	+11	52.1		
Dec. 27, 1926	2	......	....	....	....	−75%	
Jan. 7, 1927	2	128/48	100	+16	49.6		
Jan. 15, 1927	1		Operated				
Jan. 22, 1927	1	126/42	78	+12	47.7		
Mar. 14, 1927	7	108/52	71	−15	51.4		
Mar. 28, 1927	2	......	....	....	....	+50%	
April 25, 1927	4	116/58	73	−11	52.2		
June 6, 1927	6	112/58	80	+2	50.2		
to							10 tests
Dec. 1, 1927	24	110/60	88	+6	51.6		
Dec. 28, 1927	4	......	....	....	....	−50%	
Feb. 3, 1928	9	120/48	102	+17	49.0		
to							5 tests
May 4, 1928	13	138/68	88	+31	49.3		
May 18, 1928	2	130/72	96	+35	48.8		
May 24, 1928	1		Operated				
July 7, 1928	2	116/68	52	−28	54.5		
July 14, 1928	1	118/70	64	−31	55.0		
July 16, 1928	..	......	....	....	....	±0	

This patient was a young woman of 29, first seen on December 6, 1926. She presented a clear-cut outward appearance of exophthalmic goiter, was emaciated, intensely nervous, and showed all the conventional stigmata. She gave a history of good health except for a poor appetite up to the preceding July. At this time her appetite became voracious, and at the same time her friends called attention to the protrusion of the eyes. The condition progressed and in September her attention was called to the palpable thyroid enlargement. The family history that she gave was entirely irrelevant. In her own personal history, an attack of measles at the age of 4, and three or four minor infections during the preceding year, were the only points of comment. The menstrual history had been an entirely uneventful one up to a year previously. At this time the periods fell to two days and with a very scanty flow. The basal rate determination showed the normal value of +6 per cent, a pulse rate of 84, and a normal systolic and low diastolic blood pressure. As her basal rate was wholly incommensurate with her patent goiter condition, and the degree of toxicity which she exhibited, it was repeated and +11 per cent recorded. Her sugar tolerance was found to be notably low, at a level, in fact, which we had never before recorded in uncomplicated thyroid hyperactivity. Subsequently the patient became very toxic. A test on January 7 showed a basal rate of +16 per cent, progressive tachycardia and loss of weight. She was operated upon one week later, after the usual period of rest, and shortly dropped to a mild hypofunctional level. There was distinct clinical improvement and during the latter part of this period a sugar test was performed which showed a tolerance 50 per cent above prediction. For the next few months she kept in touch with the Clinic and at the end of about a year from her first contact began to give signs of a renewed toxicity, although the basal rate presented the normal value of +6 per cent. Her sugar tolerance at this time was —50 per cent. Operation was postponed, but in May of the current year it became patent that the condition was progressive with steadily increasing toxicity. A second operation was performed, and the tests since made showed a drop of the basal rate to a frank hypofunctional level, while the sugar tolerance has become normal, the patient has gained weight rapidly, the exophthalmos is greatly diminished, and the patient regards herself as entirely cured. The interesting feature in this case is the marked divergence of the sugar tolerance with the slight variations in the basal rate. This reverses completely the usual thyroid finding in which even marked over- or under-activity of the gland are accompanied by relatively slight changes in the sugar tolerance, and in approximately two-thirds of our cases by no departure from the normal. A possible explanation already touched upon could lie in the existence of a second hormone produced by the thyroid which under ordinary conditions is but slightly influenced by changes in glandular activity. In a few cases, however, this hormonic influence seems to be the one involved, that agent which controls the oxygen consumption being but slightly influenced. That the patient was toxic there can be no possible doubt. The recession of the symptoms with each of her operations, but more marked with the second, and the absence of any other disorder discernable after careful and thorough study, would seem to indicate a definite thyroid aberration as the cause of her difficulties. The suggestion offered above is no more than a suggestion. We have had, however, a few cases in the past (4 or 5) which have shown analogous abberrations of carbohydrate metabolism. In cases in which thyroid disease was definitely established and no superimposed effect could be demonstrated, the fact that, from the clinical side, individual patients will show their greatest response to thyroid extract alone, to thyroxin alone, or to a judicious blending of the two, may well be pertinent to this thesis.

CASE S-1895. This case was reported as of possible interest as demonstrating a recurrent hypothyroid condition, after a considerable interval, in a woman of advanced years. The patient presented as her chief complaints bronchial asthma which had begun after her thyroid operation; arthritis in the back and left leg, from which she had suffered for the past four years; a general itching of the body similar to that experienced previous to the operation, and which was of but brief duration; tachycardia which had developed in the past few weeks.

Family History: The father died of diabetes, the mother of cancer. Many of the immediate family were above average height. No other case of thyroid disease was recorded.

Past History: The patient reported the minor childhood diseases, but none of the graver complaints of adult years. A thyroidectomy in 1921 was her sole operation. She had recently developed what she termed a "thyroid headache" similar to that experienced previous to her operation. There had been marked loss of hair at that earlier time, and again recently. The teeth had all been removed, and there was more or less soreness in the mouth, which latter was of recent date. She complained of dyspnoea and palpitation at the two intervals significant in relation to her thyroid. She had lost 15 lbs. in the past four months. Her menstrual history was uneventful. She was very fatigable. During her long married life she had one miscarriage and had borne one child, which subsequently died of epilepsy.

Physical Examination showed a fairly well-preserved but undernourished woman of 72 whose hair was coarse and thin, no exophthalmos, teeth all gone and the buccal mucous membrane normal. There was no evidence of thyroid enlargement, there were minor abnormal sounds in the chest. Arteriosclerosis was present. There was some tachycardia and a few minor neurological findings which were not confirmed by the neurologist.

Laboratory Summary: The patient was 18 per cent underweight and significantly below her predicted lung volume. There was a hypertensive blood pressure, rapid pulse, urine showing both albumin and casts, and protein intake far below a maintenance level. The remaining findings were not strikingly significant.

Radiography of the chest showed scattered calcified nodes along the track of the large bronchi and emphysema. Both antra were obscured.

Neurological Examination noted the tremor of the hands, but gave no evidence of organic neurological lesion.

Cardiogram showed simple tachycardia with premature ventricular beats.

Chest Examination confirmed the harsh respiratory sounds over both bronchi, together with some peribronchial dullness.

Laryngological Examination gave entirely normal findings.

Discussion: The picture here is typical of a mild and, in this case, recurrent hyperthyroidism. Whether the infected antra played any part in this event must be a matter of speculation. X-ray therapy was recommended, and we understand that the patient has shown definite improvement.

CASE S-1188. The following case is typical of the recurrence of toxicity shortly after a successful operation for an initial hyperactivity. The patient's chief complaint was of nervousness and palpitaton. The former condition she dated from the birth of her only child five years before. The palpitation was noted somewhat later, but constituted an integral part of the picture. From the patient's history it was patent that the nervousness dated back to childhood and that the present complaint derived from exacerbation produced, in part, by her added domestic responsibility and, in part, from other coincident social problems.

Family History: The mother died of cancer. The remaining history was irrelevant.

Past History: Beyond measles and a tonsil and adenoid operation nine years previously, the patient's history was singularly uneventful. She had had some constipation, some nocturia, but in the main was free from illness or general complaint. She had been married for seven years, had borne the one child noted above, and had not conceived again. Her menstrual history showed an onset at 14 and a typically irregularity with both increase and diminution in the interval. The periods were fairly normal. She was found to be irritable, unreasonable, and egocentric. "In her hurry to convey an idea she talks so rapidly that the words become all jumbled together and the entire face goes into a nervous quiver."

Physical Examination: The patient was a fairly developed but distinctly emaciated woman of 33. The hands and feet perspired freely. There was no exophthalmos, but the tongue and hands showed fine tremor on extension. The thyroid was not significantly enlarged but venous pulsations were visible in the neck. The heart showed a marked systolic murmur, heard best over the pulmonic area, transmitted toward right and upward; the apex impulse was visible, there was a distinct tachycardia and a characteristic high pulse pressure. The knee jerks were slightly hyperactive.

Laboratory Summary: The patient was 29 per cent below her predicted weight and significantly below her predicted lung capacity. The basal rate was +44 per cent, with a variable and rapid pulse. A few hyaline casts were reported in the urine and there was very slight glycosuria. The urinary residual nitrogen was high. The blood was lymphoid in type.

Discussion: The patient presented a fairly typical thyrotoxicosis, and in November of 1927 a portion of the gland was removed. The basal rate, which had ranged from 40 per cent upward, promptly dropped to —10 per cent on November 11, and —12 per cent on December 8. The pulse had dropped to the low fifties; the blood pressure, while low, showed a more nearly normal pulse pressure. In April, however, of the current year there was a return of the patient's symptoms, there having been previously practically complete relief. On May 31, the basal rate was +26 per cent, with a pulse rate of 66. She had begun to lose weight rapidly. She was admitted to the hospital and with complete rest her basal rate dropped to +16 per cent. For outside reasons she decided to postpone operation for a brief time, but it is patent that there has been a recurrence of the toxicity and that a second operation in the near future is inevitable. The rapid recurrence in the case after a period of several months of seemingly complete amelioration is the noteworthy feature.

CASE S-1596. This case is cited for the reason that it presents recurrent toxicity after an earlier operation, coexisting with marked obesity. The patient's chief complaint was nervousness and tachycardia. She was also much overweight and the legs were noticeably large, which constituted a serious embarrassment to her. During the day they seemed to get larger, but were at all times disproportionately large. She dated her nervousness back about one year and had noted since its onset that there was a recurrent tightness in the throat on swallowing.

Family History: The father had died of thyroid failure and there was a history of cancer in the earlier generations.

Past History: Barring scarlet fever and measles in childhood and a susceptibility to tonsillitis, the medical history was substantially irrelevant. The catamenia began at nine, showed some irregularity with increased interval, and a gradual diminution in the length and amount of the periods. The obesity goes back to early childhood and has not been controllable by diet.

Physical Examination: The patient was a well-developed, generally obese young woman of 23. There was no exophthalmos, a very slight thyroid enlargement, marked tachycardia (140); the legs were very obese, but there was no pitting edema of either legs or ankles; the hands showed a definite tremor on extension.

Laboratory Summary: The patient's weight was 35 per cent above prediction; she showed a basal rate of 55 per cent above the normal, with a pulse rate of 122. The urine volume was normal; albumin was recorded, but the residual nitrogen fraction was normal. The blood sugar was sub-normal; the blood showed a slightly low value for the erythrocytes.

Cardiogram showed a normal function and rapid rate.

Diagnosis: A diagnosis of "toxic thyroid" was offered and the patient was operated upon with a very definite improvement in both clinical and laboratory signs. As the basal rate fell the body weight showed an upward tendency. In the past few months, however, there has been a slight loss of weight, and in May of the current year the patient showed a body weight of 85.7 kgm., a basal rate of +54 per cent, and a pulse rate of 112; in other words, practically the identical picture which she had at first presented. Operation was recommended and we are advised that a further partial thyroidectomy has been successfully performed with marked improvement in the patient.

The last two cases illustrate a fairly rapid recurrence in two definitely opposite types. In the first case (S-1188), the patient gave a history of previous glandular medication which had only served to intensify her symptoms. The second patient with her enlarged thyroid and her very definite obesity might well have been classified as a dysfunctional type, and also given thyroid medication. Fortunately, however, this did not happen. Another point of interest in the second case was the low level of the protein metabolism, taken in conjunction with the definitely hyperactive state of the thyroid.

TABLE XXI

	Pseudo-Nephritis		1	2	3	4
Case Number	B-110	B-110-a	B-560	S-1396	B-738	B-730
Diagnosis	—	—	—	—	— (surg.)	—
Sex	F	F	M	F	F	M
Age (yrs.)	53	53	11	24	52	26
Height (cm.)	157	157	134.0	152.0	176.3	190.5
Weight (kgm.)	69.5	59.0	29.1	69.0	85.0	81.9
Weight Deviation (%)	+26	+7	−10	+30	+7	*(+7)
Lung Volume Deviation (%)	−48	−44	−16	−12	−35	−26
Basal Rate Deviation (%)	−32	+35	−52	−39	(−16)	−40
Blood Pressure (mm.)	124/80	116/68	102/60	90/74	150/84	120/68
Pulse (per min.)	72	78	76	51	64	60
Temperature (deg. F.)	98.2	98.2	97.0	97.2	97.8	97.4
Alveolar CO_2 (mm.)	37	(33)	41	36	45	50
Urine Volume (cc.)	750	580	1700	1310	1230	620
Spec. Grav.	1.016	1.018	1.010	1.012	1.019	1.031
Albumin	0	0	+	0	+	0
Casts	0	0	++	0	0	0
Sugar	0	0	0	0	0	0
Total Nitrogen (gms.)	4.22	5.90	7.85	5.17	10.33	8.33
Residual Nitrogen (%)	6.5	5.0	12.9	9.5	8.5	12.4
"Urobilinogen"	0	0	0	0	0	+
Phen. Sulph. Phthal. (%)	32	55	21	32	39	48
Galac. Tol. Deviation (%)	±0	±0	+33	not done	±0	±0
Non-Protein Nitrogen (mgm.)	36	26	33	32	35	31
Uric Acid (mgm.)	4.9	3.2	2.5	3.2	3.8	3.3
Sugar (mgm.)	87	77	87	85	93	100
Haemoglobin (%)	90	95	100	85	85	90
Erythrocytes (10^6)	4.83	4.72	5.50	4.20	3.78	4.76
Leucocytes (10^3)	5.25	6.05	11.70	7.30	3.50	5.70
Neutrophiles (%)	48	51	26	49	47	56
Lymphocytes (%)	49	40	71	40	44	32
Eosinophiles (%)	0	1	0	2	3	2
Monocytes (%)	3	8	3	9	6	9
(Basophiles) (%)	0	0	0	0	0	1

*See discussion of case.
1. Presenting so-called "Epstein's Nephrosis."
2. Characteristics cardiac findings.
3. Complicated with primary anaemia.
4. Complicated with earlier hyperpituitarism spontaneously arrested.
* Sitting Height Index < 0.50.

GROUP VIII. "PSEUDO NEPHRITIS"

CASES B-110 AND 110-a. The patient's chief complaint as presented was a bloating of the face, which gradually extended over the chest and arms. This at first began some two months before admission, but probably had been going on for some time prior to this. She had been getting progressively fatigable and nervous, felt that her aural acuity was diminishing, and that there was a general failure of all of her powers.

Family History was not informative.

Past History: The patient reported all of the minor ailments of childhood and pneumonia at 36 complicated by a secondary anæmia. The deafness really began some 16 years previously, but it had been disquieting only for the last few months. She had been gaining weight recently and suffered from dyspnoea. She had always been constipated; the appetite had been poor. The marital history showed two children and two miscarriages. The catamenial history was normal, including a slow and uneventful menopause, which apparently was completed a few months before her admission.

Physical Examination: The patient was a well nourished, somewhat obese woman of 53. She presented some loss of hearing. The skin was dry, glossy, and hypertrophic; the eyelids swollen, palpebral fissures narrow; practically all teeth had been removed, those remaining being abscessed; the thyroid was not enlarged: the heart action was slightly irregular, and there was a slight systolic murmur. The remaining findings were substantially normal.

Laboratory Summary: The patient was 26 per cent overweight and had lost nearly half of her predicted lung volume. The basal rate was —32 per cent. The urine volume was scanty, elimination poor. The phthalein output was distinctly below the normal. Protein intake, as shown by the urinary nitrogen, was far below a maintenance level. The blood analysis gave evidence of lowered kidney permeability. The blood showed a marked relative lymphocytosis.

Neurological Examination showed certain paræsthesias, an 8th nerve disturbance, and a possible loss of deep sensation in the right leg.

Eye Examination showed a definite contraction of form and color fields, most pronounced in the upper quadrant, the latter due to lid droop.

X-ray Examination: The sella was normal; the heart showed right-sided enlargement.

Pelvic Examination: Findings were normal except for minor residua of child-bearing.

Discussion: The possible suggestion of primary anæmia had been ruled out by observations made elsewhere. The picture here presented was consistent with a hypothyroidism with myxedema. The patient was placed on thyroid extract, and two months later returned for a brief series of check observations. Clinically she was greatly improved. The skin had cleared entirely: she had lost 10.5 kgm. weight: the lung volume was slightly better: the phthalein output had risen to a normal level; her nitrogen elimination had improved: while the blood nitrogen values had diminished to levels consistent with her protein intake. While the blood was still lymphoid in type, the degree had diminished, and the general formula far more nearly approached the normal.

GROUP IX. THYROID FAILURE WITH MISCELLANEOUS COMPLICATIONS

CASE B-560. The patient was a boy of 11 whose case had been diagnosed as one of Epstein's nephrosis. Two series of studies were available which had been made at earlier periods. The boy was first admitted to the hospital in January, 1919, then being 4 years of age. He was kept under observation for nearly a year, and was discharged as having chronic parenchymatous nephritis. During this period he had shown marked ascites of the abdomen and, on a number of occasions, quanties of fluid of the order of a quart had been removed by tapping. The urine had shown a characteristic picture. He remained in good health until July, 1921, when he was readmitted in a markedly edematous condition. There had been vomiting for twenty-four hours. The condition progressed, and early in August a decapsulation operation was performed on the right kidney, and in September on the left. There was rapid improvement and he was discharged in November. Three years after a tonsil and adenoid operation was performed, and in March, 1925, he was again readmitted with marked edema. The condition cleared up in a few days, however, and he was discharged with a confirmation of the earlier diagnosis. He was admitted to this service in June, 1926, with marked anasarca and ascites. Again the condition gradually cleared up and in July, 1926, further study was undertaken.

Family History: A general history of renal disease was obtained.

Past History: Beyond the facts already discussed, the patient reported scarlet fever, influenza, several minor ailments, tonsilitis, and bronchitis.

Physical Examination showed a somewhat undersized boy of 11, with face somewhat full and puffy, general nutrition fair; the nose was broad and flattened, the nares not obstructed. He showed a minor cervical adenopathy, but no thyroid enlargement. The heart showed a soft systolic murmur at the apex, which was not transmitted. The lungs and abdomen substantially normal. The remaining findings were not significant.

Laboratory Summary: At the time of this examination the acute phase had passed. The urine volumes were ample, albumin and casts were both present; elimination was good; the residual nitrogen was high; the phthalein output at this time distinctly low. The boy was 10 per cent underweight and had shown a basal rate of —52 per cent. This very low level would be influenced, naturally, by any residual trapping of fluid, but as the lad was 10 per cent underweight and gave no positive evidence of the presence of fluid, the value observed was felt to be approximately correct. The blood pressure was low, the temperature slightly sub-normal. The sugar tolerance at this time was slightly above the normal. The blood constituents were normal and gave no evidence of retention. There was a slight leucocytosis, with very marked increase in the lymphocytic fraction.

X-ray Examination: The skull, sinuses, and kidneys were normal. The sella was normal, except for some evidence of bridging between the clinoids.

Eye Examination: Fine granular pigmentations throughout the retinæ ("pseudo-snuff fundi"), which is probably normal. There was a slight blind spot enlargement and a possible slight contraction of the color fields, which could not be confirmed, however, a few days later.

Studies of the urine showed no loss of concentrating power in the kidney, there being a variation of ten points. The general picture was one of renal irritation without functional damage.

Cholesterol and fibrinogen of the blood were high; plasma protein, low.

Discussion: With just recognition of the kidney condition, the remaining picture was essentially that of a thyroid failure. Part of the earlier work on this patient had been done elsewhere, and we have reason to believe that some thyroid extract had been exhibited, but no chronological record was available. On May 28, a basal determination was carried out which showed a low blood pressure, a rapid pulse, and a rate recorded as —15 per cent. As the patient was nervous, however, this could be discounted materially. On June 10, with subsiding pulse rate, the basal rate was about —50 per cent. On June 23, the pulse was above 100 and the basal rate +18 per cent. Three days later the pulse was 88 and the basal rate +11 per cent. On July 6, the pulse was 72, temperature and blood pressure definitely low, and a basal rate of —26 per cent was obtained. As will be seen in the table, the basal rate again went still lower, and then, on thyroid medication, there was a prompt return to the normal level. The patient was discharged shortly after in a greatly improved condition. We have not been able to effect a later contact, but from the fact that there have been no further hospital entries recorded it seems fair to assume that there have been no serious recurrences.

In Epstein's original papers, he lays great stress on the blood cholesterol and fibrinogen. So far as we are informed, no adequate studies have been made on the influence of thyroid failure on these substances. While this is not the place to carry out a discussion, the writers are entirely unconvinced as to the existence of the so-called Epstein nephrosis as a disease entity. Certainly in the present case there is a typical picture of thyroid failure, which is supported by the patient's very prompt response to thyroid medication. This case opens up a number of lines of study, some of which are at the present being prosecuted. Whether there be a definite relationship between kidney and thyroid function, or whether the former be influenced by the metabolic disturbance incident to hypofunction of the latter, is a question that awaits future resolution. The case is offered here only as it presents certain points of general interest.

CASE S-1396. This patient is included in the group not because she presented a complication of thyroid disease, but because of a very interesting series of cardiograms produced by her condition and subsequent medication.

The chief complaint was of nervousness and fatigability. Four years prior to admission her husband had died after one year of married life. This produced a profound emotional shock, followed by loss of weight and general nervous imbalance. One year subsequently she began to increase in weight, and this had progressed to a point of definite obesity. During the past year she had had numbness and pricking sensations in the hands and had become relatively insensitive to hot objects.

Family History: Not significant.

Past History: Beyond minor ailments of childhood, the patient's life had been medically uneventful. She did not become pregnant during her brief marital experience. She complained of some dyspnoea, constipation, and some indigestion with flatulency. She had become decidedly asocial since the onset of the present illness. The menstrual history showed a normal onset, but with marked irregularity, the periods occurring from two to three months. The periods themselves were somewhat profuse.

Physical Examination: The patient was a well-developed, obese young woman of 24, presenting the typical facies of myxedema. The hair on the vertex was dark and very scanty, the skin very tough, thick, dry and scaly; palpebral fissures greatly narrowed, eyelids puffy. There was pain on pressure over the right maxillary sinus. The blood pressure was low and there was a marked bradycardia (44). A few scattered rales were reported in the right chest. There was some tenderness in both lower quadrants. The remaining findings were not signficant.

Laboratory Summary: The patient was much overweight. The basal rate was —39 per cent, with very low blood pressure, bradycardia and subnormal temperature. The urine was substantially normal except for poor elimination and high residual nitrogen. Her protein intake was inadequate. The blood showed a definite lymphocytosis.

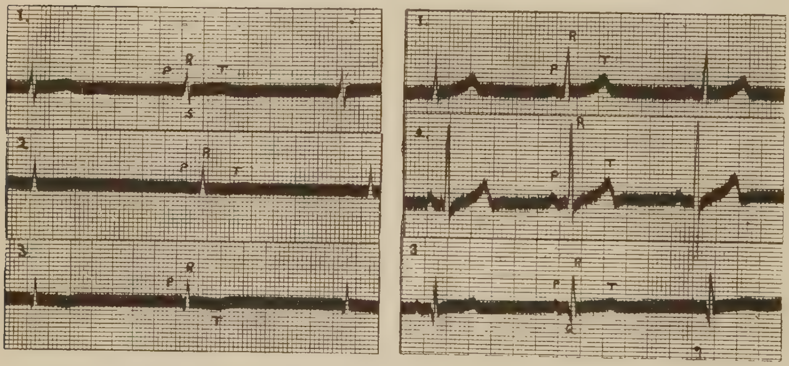
X-ray Examination: Chest, heart and lungs were normal. The teeth showed one unerupted molar and one periapical abscess. The skull was normal.

Pelvic Examination: The findings were normal. The tenderness in the lower quadrants was not confirmed.

Cardiogram: The graph apparently showed a normal mechanism at a retarded rate (see plate).

PLATE VI

Case S-1396. Cardiograms before and after treatment.



March 1, 1927 April 27, 1927

Audiogram: Normal conditions were found.

Laryngological Examination: Tonsils were suspected, but infection could not be demonstrated.

Neurological Examination: Conditions were normal except for findings associated with the myxedema.

Eye Examination: The form and color fields very markedly contracted symmetrically; the blind spots, much enlarged.

TABLE XXI-a

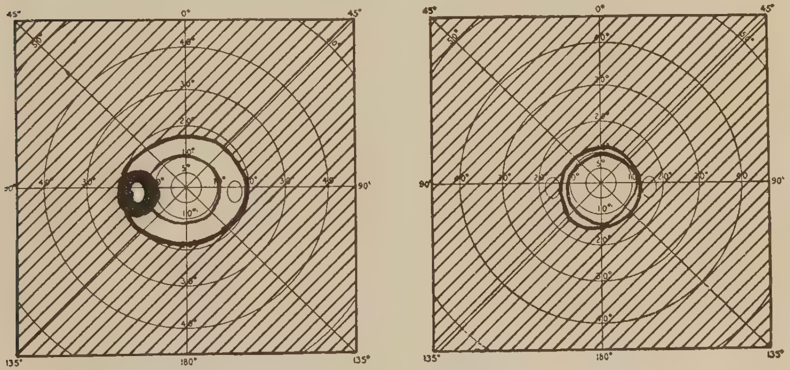
CONTINUOUS RECORD OF CASE OF HYPOTHYROIDISM

Date	Basal Metabolism	Blood Pressure	Pulse	Weight
March 1.............	—39%	90/74	51	69.0
15.............	Began medication			
April 2.............	—11%	102/66	50	62.3
9.............	—10%	96/50	48	60.5
	Lowered dose			
18.............	—19%	90/38	46	58.5
	Increased dose			
23.............	—11%	86/38	44	58.4
30.............	—10%	94/42	52	57.3
May 16.............	— 4%	98/54	54	57.5
21.............	— 3%	98/54	58	57.5

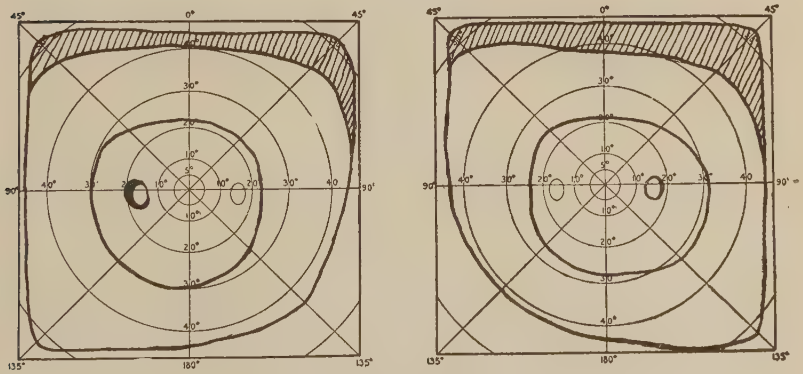
Discussion: The patient presented a typical picture of hypothyroidism with myxedema. She was placed on thyroid medication and in a few weeks obtained a normal basal rate, with the loss of slightly more than 10 kgm (see table). Clinically, she showed the remarkable improvement which may be confidently anticipated in simple cases of thyroid failure. The cardiogram became entirely normal (see plate). An interesting feature was the persistence of the low blood pressure and bradycardia after all of the other findings had become normal. A second eye examination was made and the earlier much contracted fields found to have been entirely corrected except for a slight upper field cutting, due to lid droop (see plate).

Plate VII

Case S-1396. Eye plots before and after treatment.



March 5, 1927



September 28, 1927

Case B-738. The patient's chief complaint was of asthenia, which first became remarkable 2 years ago. It had been progressive, and during the preceding four months had become seriously crippling. A diagnosis of thyroid failure had been made, but no thyroid medication had been given. About four months ago she began to experience numbness and stinging in the extremities, and this had spread somewhat to involve the entire limb. For five years past she has had more or less trouble with eczema. Recently the blood calcium was found to be deficient and iron injections were given.

Family History was not significant.

Past History: The patient had minor ailments in childhood, and in 1907 a partial thyroidectomy. In 1918 the uterus was removed and an appendectomy was done. For the last 2 years there had been almost constant headache. The hair had grown gray and become very dry during the same interval. The eyes were easily fatigable. During the last year she had developed a rash in the mouth, and at times small ulcers with white centers had appeared on the tongue. There was occasional dyspnoea, a tendency to constipation and flatulency. The patient was unmarried; the menstrual history was substantially negative except for scanty periods and termination with the fibroid operation above referred to. Recently she had experienced coldness of the extremities and some edema.

Physical Examination: The patient was a well-developed and well-nourished woman of 52, somewhat above the average height. She exhibited a moderate exophthalmos and a vesicular eruption on the tongue. The skin was dry and hypertrophic throughout, with eczematous patches on the extremities; brown macular eruptions were observed on both legs. There was a slight, coarse tremor of the hands and the reflexes were sluggish.

Laboratory Summary: The patient was 7 per cent overweight. The basal rate as recorded was —16 per cent, but this was probably somewhat above the truth. The blood pressure was slightly high. The urine showed albumin, and the residual nitrogen an upward tendency. The sugar tolerance was normal. The blood analysis gave no evidence of retention. The blood morphology showed an anæmia of the primary type with a leukopenia.

Skin Examination defined a papulo-vesicular eczema and suggested that the pigment areas were due to Schamberg's disease.

Neurological Examination demonstrated loss of bone conduction in the lower extremities and noted the paræsthesias already recorded.

X-ray findings of the skull and sella were normal.

Eye Examination: The fundi showed a slight amount of vascular sclerosis; there was cutting of the upper form fields, due to lid droop.

Neutral Red Test: Dye was not recovered in two hours.

Gastric Analysis: No free hydrochloric acid was found.

Diagnosis: The patient presented a post-operative hypothyroidism complicated by a primary anæmia. The latter was shown to be in a state of remission, with characteristic regeneration, as evidenced by repeated typical blood examinations.

CASE B-730. This case presents several points of interest, as a current endocrinopathy is complicated by residua of an earlier and different endocrine disease.

The patient's chief complaint as given was of pain in the back, from which he had suffered for three or four weeks, and which followed a period of hard manual labor. As a matter of fact, the patient was sent in for the evaluation of certain physical abnormalities, coupled with a definite mental arrest.

Family History: Irrelevant.

Past History: The patient reported minor ailments, smallpox at 21 (there having been an unsuccessful vaccination at the age of 18), several traumatic injuries not germane to the present study. He had had severe frontal headaches for the past year. All of his teeth were removed at the age of 22 because of severe caries. Prior to this, there was almost daily toothache. Up to the age of 16 he was of normal size. He then began to grow rapidly and in a relatively short time reached his present height of 190.5 cm., which is probably greater, as the patient's posture is poor and he exhibits a definite stoop. He complained of an occasional fleeting pain lasting only a minute or two in the upper right quadrant.

Physical Examination: The patient was a noticeably tall, somewhat spare young man, 26 years of age. There was some enlargement of the frontal bossæ and a definite protrusion of the lower jaw. The teeth, as noted above, were all missing. The tonsils were enlarged, and there was a slight thyroid enlargement. In addition, a slight inguinal and cervical adenopathy was noted. The testicles were somewhat atrophic, the skin dry, the posture, as noted above, was poor. Mentally, the patient was slow and immature and definitely below an average intelligence. He further presented a speech difficulty, articulation being thick and obscure.

Laboratory Summary: By the Dreyer standard, the patient was 7 per cent overweight, but as the sitting height index is slightly less than 0.50, he was actually slightly underweight. There was some loss of predicted lung volume. The basal rate was —40 per cent, with a tendency to lowered blood pressure and bradycardia less clearly shown in the present than in other records. The temperature was slightly subnormal. There was oliguria, a high residual nitrogen, and a somewhat low phthalein output. The sugar tolerance was normal; blood constituents normal; a blood morphology, substantially normal.

Cardiogram: This shows a normal mechanism with simple bradycardia (pulse rate 51).

X-ray Examination: The skull, sinuses, and sella were normal.

Audiogram: Slight general loss of hearing in both ears was noted.

Eye Examination: The discs were yellow, the blind spots greatly enlarged, and both form and color fields notably contracted symmetrically.

Duodenal Function (McClure): The values were all low, indicating a definitely disturbed liver function.

Icteric Index was high.

Van den Bergh: A strongly positive reaction was obtained.

Discussion: This is a case in which the findings are susceptible of several possible interpretations. Its resolution must rest on the basis of probability. The patient's outward habitus is, of course, suggestive of a pituitary overactivity. That such a condition obtained, we believe there can be no question, and, equally, that there was a spontaneous arrest some years before we saw the patient, which left the gland at a present normal level. While it is true that the pituitary could be in a functional transition from an initial hyper- to a terminal hypo-active state, there is nothing in the present study to support such a theory. The level of the basal rate, the bradycardia, the oliguria, coupled with the absence of a high blood uric acid and an eosinophilia, are all observations against a pituitary diagnosis. True, there is a positive urobilinogen test, but the demonstrated dysfunction of the liver offers a direct cause for its appearance. It should be further noted here that we do not always find changed sugar tolerance with liver dysfunction. That this should be so is to be expected, in view of the large number of wholly divergent causes which produce a picture significant of disturbed liver function. The storage and metabolism of sugar by the liver is but one of its many functions. That some of these may be profoundly disturbed without producing correlative changes in all, is too patent to require discussion. The patient's atrophic testicles play no part in the picture. We have shown that ablation of the testicles in adult years will not affect significantly any of the objective findings of the complete laboratory analysis. The diagnosis on this patient is a current thyroid failure coupled with some measure of liver dysfunction. The physical habitus of the patient reflects an earlier endocrinopathy involving the pituitary which has ceased to be actively operative.

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STUDIES OF THE ENDOCRINE GLANDS

IV. The Male and Female Gonads

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In a series of papers from this institution, a general method for the diagnosis of endocrine disorders has been described in detail (1) and the results obtained from its application to pituitary and thyroid malfunctions presented (2) (3).

This paper summarizes our results with cases showing aberrations of the primary sexual organs, the testicles and ovaries. In presenting this material, the authors earnestly desire to avoid the controversial element which has operated greatly to enlarge if not enrich the literature. To that end only the observed facts will be presented, with such conclusions as are directly warranted. Certain of our findings are distinctly unorthodox in relation to more or less generally accepted theory, and it is felt that the actual data will be more significant if unembellished with a mass of supporting polemic.

The enormous social and economic import of the exocrine functions of these glands, coupled with the usual assumption of interdependence upon the internal secretory activities, has inevitably colored thought and influenced trends of study. From earliest record, speculation has endowed the sex organs with a multitude of attributes basic to the whole scheme of existence. It remained for Brown Séquard to render concrete the surmises of Berthold—or even Bordeu, to make the happy alliteration complete—and realize an acceptable recrudescence of the best traditions of Egyptian mysticism and medieval alchemy. The influence of sex upon physical and mental habitus has long been recognized. Emasculation practised in man in conformity with various religious beliefs and in the domestic animals for economic reasons, derives from a remote antiquity. The striking outward differences that pertain to sex in the higher forms of life and their modification by ablation of the sex glands, must early have been recognized, and as a result castration was practised to confirm certain qualities that unchecked maturation would have destroyed. Sex and reproduction are not identical, though the latter depends upon the former in the more evolved forms of life. Sex implies phylogenetic differentiation; reproduction, the fusion of the differentiated parts. It is the external manifestations which are the prime factor in reproduction which is, after all, the one essential. But conservative interpretation of experimental evidence regards a concomitant endocrine function as one essential for the proper development of those portions in which the outward capacities have their origin. Other equally potent endocrine agencies must likewise be admitted if current belief as to the genesis of pubertas praecox and kindred developmental anomalies be accepted. The more expansive—and less critical—views that merge in the function of the sex organs, the gamut of physical and mental characteristics of man, do not require discussion. The due sequence of the stadia of development leading first to maturity and later to the recessions incident to the decline of reproductive power are intrinsic, seemingly, in the proper functional adjustments, not only of the gonads themselves but of a number of other centers of endocrine activity. The genital arrests of pituitary and thyroid failure do not, a priori, connote a simultaneous loss of internal secretory function on the part of the testicle or the ovary. Ablation of the gland with the removal of those cells which are usually assumed to be the seat of endocrine activity, also robs the organism of those in which the external function is engendered. The data from incomplete supressions such as the subjects of x-ray sterilization, vasectomies and salpingectomies, and from cryptorchids, are inconclusive, since the sterilities may be no more than mechanical interferences. The degenerative changes apprehensible by careful histological examination do not exclude rigorously all traces of the parts of exocrine function. When one realizes how fractional residua are capable of maintaining function, it would seem wise to maintain a genial scepticism toward the comprehensive generalizations based on partial experiments. Transplantation studies suffer from the same objection as those involving complete ablation, since all portions of the gland participate in the experiment. While striking results are obtained, the lower animal species seems to play the predominant part in the phenomena evoked, the sexes being unequally and not uniformly influenced in those groups where changes are demonstrable. The use of organ extracts offers perhaps the most definite potentiality, but here again the presence of extraneous active material on the one hand, or the destruction of the active principle during extraction on the other, places obstacles in the way of unqualified success. That these are in fair way to be overcome, would seem to be certain from the success that has attended the studies with others of the endocrine group. But even here a temperate conservatism must be observed. Striking as have been the results with rats and mice by the use of ''follicular hormone'' the alleged excitation of oestrus in the spayed female with extracts of testicles and other foreign substances raises a natural question as to the specific character of the phenomenon. A detailed recountal of the difficulties attending the solution of these several problems lies outside the scope of the present thesis.

To summarize the facts pertinent to this discussion, it may be said that the primary sex organs have respective exocrine functions from which the reproduction of the species derives. Further, there is evidence of an internal secretory function of the primary sex organs, well established in the female and probable in the male, at least in the years preceding maturity. Man, generically speaking, passes through three well defined periods of existence,* determined by the power of reproduction. In the female there is possibly a further subdivision intrinsic in the oestrous cycle and the immediate results of reproduction as manifested by pregnancy and lactation. These are, however, but incidental to her period of fertility, and merge in it in a general classification. During the first of these, the period of growth, many processes are going on in the body in which an endocrine activity of the gonads may or may not be involved. From the results of castration in this period† there would seem to be abundant evidence that such loss to the growing organism induces gross somatic changes of an unmistakable character.

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*Lipschütz (4) denies this.

†The observations are based wholly on the male. The results of prepubertal castration in females is recorded only by Roberts [cited by Marshall (5)], and but little credence is attached to his reports.

Castration in adult years of both males and females is a common surgical procedure. Inversion of outward sex habitus is the common report although the somatic changes are less striking, as growth possibilities, at least of the bony structures, are definitely restricted. Castration in advanced years is attended by less striking changes though the development of marked hirsuties in aged females is, at times, referred to as a manifestation of a "physiological castration" implying suppression of ovarian function as an incident of the degenerative changes of senility.

Fundamentally, the sexes are sharply differentiated,* although many cases of apparently indeterminate sex are recorded in the literature and these must represent but a small part of existing cases. The multiplicity of genital anomalies producing this end result is not to be wondered at when embryonal relationships are considered. For example, in the series of nearly two thousand cases from which the present group are excerpted, there were three complete visceral inverts, a more comprehensive developmental aberration than hypospadias or analogous conditions which contribute so large a proportion of the pseudohermaphrodites. In dealing with the gonads then, it is necessary to treat them separately, as organically and functionally they are completely differentiated structures. Furthermore, the ovary is seemingly concerned, directly or indirectly, with a large number of important functions incident to reproduction, which find no correlative activities in the male. Finally, in the corpus luteum the ovary develops transiently a new potential source of endocrine activity seemingly independent of the other portions of the gland.

Needless to say, from any center in which a wide variety of functions find their origin, changes may occur which will influence some but not all of the several activities. To illustrate, the functional level of activity of the ovary during pregnancy remains a matter of speculation. By many, an overactivity is inferred, while others see a period of quiescence with lessened functional level. Thus we may expect widely divergent pictures in the three phases of life as conditioned by reproductive activity. That the immature child should offer the same evidences as the adult is possible but not probable. Even though we concede—as is not usually done—that the reproductive mechanism is entirely independent of the normal endocrine activities of the gland, the establishment of new functions in one set of cells would seemingly influence, even though by indirection, the behavior of other cells immediately adjacent to them. The problem then is admittedly intricate, and only by limiting the variables so far as one may is it possible to arrive even at a first approximation.

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*In Neugebauer's (6) exhaustive compilation but five cases of true hermaphroditism are recorded [see Garre (7), Simon (8), Pick (9), v. Salen (10), Schickle (11), and Unger (12)] and in each of these only a single ovotestis was demonstrated, the other being unitary organ. The few other alleged cases recorded are lacking in positive demonstration. More recently, Neumann (12a) has compiled a number of cases from the more recent literature. Of the ten where ample description was available to him, he regards four at least as doubtful. An eleventh [Berblinger's (b) case] was described only in a note and cannot be passed upon. Of the six which he accepts, only one (Robert Meyer) (c) shows bilateral ovotestes. He cites an additional ten from foreign literature not to him available, of which two are doubtfully authentic, two [Briau, Lacassagne & Lagouette (d), Masson (e)] are bilateral ovotestes, and the remainder range from Burden's (f) amply provided individual with an ovary and a testicle on each side, to the more modest equipment of Baldwin's (g) patient with a left ovary and right testicle.

The cases reported here, with but non-significant exception, are adults. Work with children in the prepubertal period calls for other standards, at present imperfectly defined, and in some cases even for other methods of approach. All of the women here reported had established the catamenia, and but two of the males were immature. The inclusion of these, as will be shown later, has larger measure of warrant than would be the case with the opposite sex. Post-menopausal cases appear among the women, as the differences in this stadium are of degree rather than of kind.

Another point requiring amplification is the designation of all of the cases as "hypofunctional." The literature contains frequent reference to a hypergonad state. We have never been privilege to see such a condition. Unquestioned hypofunction is produced by castration, and the study of a group of such cases defines a clinical and laboratory picture of fairly clear-cut outline. The antithesis of this picture we have never seen. Pubertas praecox cannot be regarded as a hypergonad state, particularly if we accept the alleged influence of other endocrine entities as causative. It becomes, under these conditions, an interesting but resultant developmental anomaly to be contrasted with the arrests engendered by pituitary and thyroid failure. A libido in excess of the usual conventional standard is certainly no warrant for the assumption of a hypergenital condition. Even conventional standards vary and some allowance must always be made for the personal factor operative in normality. Further, it is well known that libido persists, sometimes for long periods, in individuals who have lost the primary sex organs in adult years. If libido be the criterion of gonad activity, we have in this fact a most uncompromising contradiction. The fact is that the assignment of restrictive limits to the normality of the sex urge is on a parity with other ex cathedra utterances unhampered by a paucity of basic fact. And above all, the fact remains that in a considerable group of individuals referred for study as hypergonad cases, not one has even suggested a clinical and laboratory picture the opposite of that produced by castration.

TABLE I
PHYSICAL MEASUREMENTS

Observation		Male	Female	Remarks
Number of Cases		**11**	**189**	Total=200
Distribution	%	**5.5**	**94.5**	
Age (yrs.)	High	77	68	
	Low	10	14	
	Average	**34**	**34**	
Height (cm.)	High	175	175	
	Low	146	140.5	
	Average	**166**	**161**	
Sitting Height (cm).	High	93	94	
	Low	75	75.5	
	Average	**88**	**86**	
Sitting Height Index		**0.530**	**0.534**	
Chest (cm.)	High	99	121	
	Low	79	60	
	Average	**87**	**77**	
Trunk Chest Index		**1.010**	**1.117**	
Weight (kgm.)	High	80.7	124.0	
	Low	50.5	35.8	
	Average	**64.4**	**60.4**	
Area (sq. m.)	Average	**1.72**	**1.64**	
Lung Volume (c.c.)	High	4940	4000	
	Low	1800	930	
	Average	**3710**	**2600**	

Obviously, as no "hyper" state can be defined, the intermediate zone of dysfunction becomes equally impossible to designate. True, all disturbances of the endocrine glands might be termed dysfunctions, as is from time to time suggested. But with such clear-cut and sharply differentiated entities as are presented by the thyroid and pituitary for example, it bespeaks a meticulous rather than a scientific caution to insist on a carefully non-descriptive classification.

As all of our cases accord in kind, though not in degree, with the results produced by complete ablation of the sex glands, we feel warranted in designating them as hypofunctional in character.

With these introductory remarks, presented to define a position and not to excite acrimony, we may turn to the consideration of the data of the several observations. Following the sequence of the earlier papers, we may first take up the physical measurements and certain related statistics. These have been collected in Table I.

The sex disproportion is striking, and as a statistic may be misleading. Pathological changes in the testicles are seemingly of less frequent occurrence than in the ovary. Our figures probably represent a trend rather than a definition. There is a wide span of age, but as has already been noted, the prepubertal element is practically absent.

TABLE I-a

AGE DISTRIBUTION

Years	%
11-20	13.5
21-30	37.5
31-40	22
41-50	18
51-60	6
61-70	3

Only six of the women were less than eighteen, (two at fourteen and sixteen, one each at fifteen and seventeen) and, as before stated, menstruation had been established in every case in this group. This exocrine sign of maturity is conventional but is probably the best criterion to adopt. The absence of the male, castrated in prepubertal years, eliminates the abnormally tall adult eunuch, and the average height recorded compares well with usual normal standards. The women are equally not remarkable.

Sitting height indices show no departure from the normal, and the several other measurements might easily represent those of a group of healthy average individuals. The authors recognize that the elimination of the prepubertal case exercises an influence, but were they included, for proper presentation they would fall in a separate category and so be without influence on the data as presented. The arbitrary inclusion of a group of children with the adults would synthesize an artefactual relationship that would be meaningless.

While the raw data of actual measurement have true significance, relationships of the individual to some established standard indicate a trend more strikingly. The use of the Dreyer and West standards, under limits already defined (13), offers a basis for one such comparison.

TABLE II

"VITAL CAPACITY" OBSERVATIONS

Observation		Male	Female
Weight	High	+34%	+107%
	Low	−15%	−41%
	+Average	+18%	+22%
	%	60	51
	−Average	−10%	−12%
	%	40	49
	Net Average	+7%	+5%
Chest	High	+19%	+66%
	Low	−2%	−19%
	+Average	+9%	+12%
	%	60	47
	−Average	−2%	−7%
	%	40	53
	Net Average	+4%	+2%
Lung Volume	High	+14%	+23%
	Low	−58%	−67%
	+Average	+9%	+6%
	%	40	11
	−Average	−17%	−22%
	%	60	89
	Net Average	−7%	−19%

The few males vary within far more restricted limits than do the females. This may result from the paucity of observations in the male series. Certainly there is not apparent that tendency to obesity that is considered a cardinal evidence of gonad failure. Tandler and Grosz (14) recognize two types of eunuch, the "tall" and the "fat," and consider that these repeat in the eunuchoid group. In this series there is obviously not enough obesity to conform to the one, and the heights recorded in Table I eliminate the other. In other words, neither by castration nor by destruction of gland function by disease in adult years, is the typical habitus of the prepubertal castrate necessarily realized. Numerous other records show that in a percentage of cases they do conform, but the observation may well be a result of extraneous causes. Certainly in this carefully studied group there is no defined tendency toward a typical obesity. On the other hand, the majority of the cases fell within the limits of a relative normality. The chest repeats the weight comparisons, as naturally could be predicted. The lung volume comparisons show a definite sex difference. The men are compared to Dreyer's standard "A," comprising athletes, soldiers, sailors, and active outdoor workers. The male gonad failures average but 7 per cent below this rather rigid standard, though the constituent members were not engaged in the active pursuits of Dreyer's classification. The women, on the other hand, are compared with Dreyer's female standard "B," and even under these more elastic conditions, fall, on the average, 19 per cent below prediction. Any impairment of normal vigor tends to be reflected moderately in this measurement. The striking feature is the relatively normal performance of the men.

The data from certain urine examinations are presented in Table III.

TABLE III

URINE MEASUREMENTS

Observation		Unit	Male	Female
Volume	High	c.c.	1440	3000
	Low	c.c.	460	230
	Average	c.c.	**1120**	**1130**
Spec. Grav.	High		1.032	1.035
	Low		1.011	1.005
	Average		**1.021**	**1.019**
Albumin		%	**9**	**27**
Casts		%	**9**	**19**
Sugar		%	**0**	**23**
"Urobilinogen"		%	**0**	**0**
Amylase Index	Av.		**18**	**16**
Salol	Av.	min.	**75**	**81**
Urea Curve	Normal	%	60	54
	Delayed	%	0	24
	Progressive	%	0	6
	Low	%	40	16
Phenol Sulphone Phthalein 2 hour Elim.	Av.	%	**51**	**55**

The sex differences here in the main are slight. A possible exception is the seemingly greater incidence of renal disturbance in the female group, an expression conceivably of nutritive disturbance of the kidney. The one salient difference is the appearance of glycosuria in nearly one-fourth of the female cases, it being totally absent from the other group. This will be discussed at length in the section devoted to carbohydrate tolerance.

In spite of the evidences of kidney disturbance, the phthalein test shows a slightly higher value for the women. The difference is scarcely significant. To summarize the data of this table, the men show a uniform normality that is somewhat striking, while the chief aberrations of the female group lie in certain evidences of a kidney disorder, which may well be referable to a disturbance of nutrition and in a frequent slight glycosuria. The nitrogen partition data given in Table IV but repeat the first indications. High risidual nitrogen has been previously shown to be associated with metabolic disturbance of endocrine and non-endocrine regulators. In the present case, the percentage of male cases exceeding the conventional limit of 9 per cent is less than in a series of non-endocrine disorders. The female group equates in frequency with the pituitary and the thyroid groups, falling short only of the adrenal, with which superimposed nephritis is almost concomitant. Further, the male average is well below, the female slightly above the limiting value that our experience has established. That hypogonadism in the female engenders certain metabolic disturbances, is the only conclusion that one may draw. The inevitable corollary is that the testicle gives no evidence in these studies of a similar influence.

TABLE IV

NITROGEN PARTITION

Observation		Unit	Male	Female
Total Nitrogen	Av.	Gms.	11.34	8.46
Urea Nitrogen	Av.	%	83.6	80.3
Uric Acid Nitrogen	Av.	%	1.9	2.1
Ammonia Nitrogen	Av.	%	2.8	4.0
Creatinin Nitrogen	Av.	%	4.3	4.5
Residual Nitrogen	Av.	%	7.4	9.1
% = or > 9.0%		%	36	48

The blood chemistry naturally equates with the urine findings, being the source from which the latter originates. Certain of the results are grouped in Table V.

At first sight it would seem as if the blood findings of the male presented an opposite picture from those of the urine. All the nitrogenous constituents are higher, and in the case of the

TABLE V

BLOOD CHEMISTRY (AND SEROLOGY)

Observation		Unit	Male(1)	Female	
Non-Protein Nitrogen	Average	mgm.	**36**	**31**	
% > 35 mgm.		%	36	14	
Urea Nitrogen	Average	mgm.	**16**	**14**	
% > 17 mgm.		%	27	16	
Uric Acid	Average	mgm.	**3.6**	**3.2**	
Net (2) % > 4.0 mgm.		%	11	8	Total Average =8%
Creatinin	Average	mgm.	**1.7**	**1.5**	
Residual Nitrogen	Average	mgm.	**18.1**	**15.3**	
Sugar	Average	mgm.	**95**	**96**	
% > 120 mgm.		%	0	3	
% < 80 mgm.		%	0	6	
+ Wassermann		%	0	2	
+ Kahn (presumptive)		number	0	0(3)	
+ Spinal Fluid		number	0	0	
+ Schwartz-McNeil		number	0	0	

(1) While the figures for blood nitrogen are influenced by the inclusion of the two nephritics, the upward tendency is still manifest if their data are omitted.
(2) All demonstrated cases of gout and nephritis have been deleted.
(3) Test not applied to two patients with positive wassermann.

non-protein nitrogen, exceed slightly the usual normal limit. The inclusion of two nephritics plays some part, but there is an upward tendency even when their data are omitted. It may be remembered that the average nitrogen elimination of the male group was one-third greater than that for the female moiety. This too would exercise some influence but not enough to account for the disparity recorded. The really significant datum is the residual nitrogen fraction, and here a definite increase is unquestionably manifest. Omitting the nephritics, it still falls slightly above the conventional limits (15 ± 2 mgm.) of the normal. In this observation we find the first real evidence of a metabolic disturbance dependent upon deranged testicular function. Blood sugar levels exhibit no sex difference, and the averages are not only rigorously normal, but the composing members almost equally so. All of the males showed entirely normal blood sugar levels which, coupled with the complete absence of glycosuria in the cases of this group, would imply an absence of testicular influence on the carbohydrate metabolism. The few females showing values above 120 mgm. reached only a maximum observed level of 125 mgm. That an emotional response may have conditioned some of the higher figures, is highly probable. Similarly, in the group falling below 80 mgm., the inferior limit was at 75, and the average for the group, 77 mgm., a decrease of very modest proportions. The significant point in this connection is the association of a strictly normal blood sugar with the observation earlier recorded of glycosuria in nearly one-fourth of the female cases. This will be touched upon in the later discussion on carbohydrate metabolism. Before leaving these data, attention is called to the normal level of the blood uric acid throughout the series, a point of significance in the differential diagnosis of endocrine disorders, as has been shown previously. It will be noted that two positive Wassermans (1 per cent) are reported in the series. Both of these subjects were surgical castrates, and the luetic element could be regarded only as a non-endocrine disease superimposed on an established hypogonadism. On this ground, their inclusion was felt to be warrantable. Incidentally, the findings in one case agreed exactly with those of the uncomplicated castrates, and in the other, only the sugar tolerance departed from the usual finding.

The blood morphology of the two groups offers certain points of interest.

TABLE VI

BLOOD MORPHOLOGY

Observation	Unit	Male	Female
Haemoglobin ....Av.	%	**90**	**88**
Erythrocytes ....Av.	10^6	**5.12**	**4.84**
Color Index....................		0.88	0.91
Leucocytes ....Ave.	10^3	**8.0**	**7.6**
P. M. N. Neutrophiles........Av.	%	**58**	**57**
% = or > 75%............	%	9	4
Lymphocytes ....Av.	%	**35**	**35**
% = or > 33%.............	%	55	56
Eosinophiles ....Av.	%	**2**	**2**
Net (1) % = or > 3%.......	%	27	21
Monocytes ....Av.	%	**5**	**6**

(1) Cases have been deleted in which a non-endocrine cause of eosinophilia has been demonstrated.

The general examination reflects the normal sex differences, the absolute values being substantially normal throughout. The differential count shows, on the one hand, no sex difference, and on the other, that slight upward tendency to the lymphocyte fraction which has already been noted in connection both with other endocrine malfunctions and also a group of non-endocrine disorders. Borchardt (15) and Sauer (16) have also both commented on a general incidence of lymphocytosis in all endocrine disorders. Antonelli (17) observed that castration in dogs lowered haemoglobin, both red and white cells and was coupled with lymphocytosis; the latter observation was confirmed by Hermann (18) after ovariectomy. Naegeli (19) regards the characteristic picture of chlorosis as dependent on ovarian failure. He was, however, unable to determine a chlorosis in a ten-year observation of a young woman castrated at seventeen to correct a "moral insanity." The ovaries were normal and the patient had matured before the operation, however. Guggenheim (20) reports lymphocytosis in eunuchoids, and Falta (21) recognizes a constant increase of monocytes. A tendency toward a slight eosinophilia is evident, although the average value falls within normal limits. Generally speaking, the blood picture presents nothing remarkable.

The respiratory metabolism, with its concomitant measurements, has claimed a somewhat larger measure of attention.

TABLE VII

Respiratory Metabolism

Observation		Unit	Male	Female
Basal Metabolism—				
Deviation	High	%	−1	+9(1)
	Low	%	−20	−25
	+ Average	%	−	**+4**(1)
	%	%	0	7(1)
	− Average	%	**−11**	**−13**
	%	%	100	93
% above +10%		%	0	0
% between +10% and −9%		%	36	36
% = or below −10%		%	64	64
Blood Pressure	Systolic Average	mm.	**109**	**111**(1)
	% < 110 mm.	%	73	62
	Diastolic Average	mm.	**65**	**69**(1)
	% < 65 mm.	%	73	15
Pulse Rate	Average	per min.	**67**	**75**(1)
% = or < 70		%	73	31
Respiration Rate	Average	per min.	**15**	**16**
% = or < 10		%	9	9
Temperature		deg. F.	**98.0**	**98.1**
Alveolar CO_2	Average	mm.	**41**	**35**
% > 35 mm.		%	91	60
% = or < 30 mm.		%	0	26

(1) The positive basal rates in this group are somewhat questionable, as the nervous element cannot be wholly eliminated. Certain other observations are likewise influenced by this factor. The determinations were made with the utmost care and the data may be regarded as representative for this type of case.

Only the effects of castration need be considered in detail. The ignorance of functional level during pregnancy, indicated by the contrary opinions that have been offered, eliminates this state from present consideration.* The influence of menstruation is likewise not pertinent, as it interjects one more element of variation which is not yet clearly related to the internal secretory activities of the gland. The general, but by no means universal, impression seems to be that there is a slight increase during the period. From another standpoint, there is no ground, a priori, for the assumption that the menopause should condition any change. The cessation of the exocrine function of the gland certainly does not prove a like inhibition of internal secretion. The applicability of the Harris-Benedict (24) equation for women, and the Aub-duBois (25) generalization, have been verified by us with a number of normal women well past the menopause.* Turning to the results of castration, Zuntz's (26) reports can at once be discarded, since his patients were not in a basal state. Curatulo and Tarulli (27), Loewy and Richter (28), Murlin and Bailey (29), Kojima (30), Angolitti (31), Heymans (32), Korenchevskii (33), and Tsubura (34), all report animal experiments in which castration produced a lowering of the basal rate in moderate degree. Lüthje (35) observed no change but his animals were not basal. Bertschi (36) with Asher could find no difference in castrated animals of either sex. Gräfe (37) in 1923 concludes that only exceptionally will ablation or loss of function produce a lowering of the basal rate, an opinion in which duBois (38) seemingly concurs. Plaut and Timm (39) report a temporary lowering, but as their "castration" is produced by x-ray sterilization, the observations hardly equate with the foregoing records, nor do they seem to warrant the rather comprehensive generalizations which the authors offer. Critical analysis of their results would lead to conclusions quite other than those presented. To summarize, it may be said that existing evidence is contradictory and opinion divided.

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*One of us (22) has shown in an extended study that the average basal rate shows a progressive increase during this condition, exceeding that determined by increased body weight (from —8 to +8 per cent during the last thirty-six weeks). Sandiford's (23) explanation that this increase represents the foetal surface contribution, invokes uncertain extrapolation, and is based on the study of a single case.

The data of our own series would seem to demonstrate a slight but unmistakable depression of the respiratory metabolism. In the group of castrated women without other demonstrable complication, the values range from —7 per cent to —23 per cent, the average of the group being —14 per cent, or substantially that of the entire series. The data of the complementary male group show an average of only —8 per cent, less than that of the complete male series. The limited number of the male cases, however, precludes a generalization which is warranted in the female series. A further point which bears directly on the observed magnitudes is implied in the foot note of the table. It has been our experience that the women presenting gonad failure exhibit, in a peculiar and marked degree, a quality of nervous tension and irritability (v. i.). Basal tests with them are far less satisfactory than with any other type of endocrine failure. An inability to remain absolutely quiet for even the period of a basal rate determination is frequently remarked, and this destroys the absolute basality of the measurements. While all observed basal rates determined by open or closed circuit methods are to be regarded as maxima*, in our opinion, the nervous instability of the female hypogonad is more likely to assume detrimental magnitudes than in any other condition studied. It must be remembered further that this source of error operates uniformly irrespective of the method used. Benedict and Benedict (40) have called attention to the serious error which may result from even minor muscular activity, and our own experience amply confirms their conclusion. The same disturbing element is operative in blood pressure and pulse rate measurements. These effects are too well known to require comment. Loss of function of the gonads would seem to depress blood pressure in both sexes, and possibly the pulse rate in the male. Averages are conceivably misleading, as has already been pointed out, and the relatively large number of female hypogonads exhibiting hypotension of a significant degree, is concealed in this necessary form of presentation. As a matter of fact, 62 per cent of the female series showed systolic blood pressures below 110 mm., and many of these were below 100. The definite lowering of the male blood pressure is seemingly a tangible evidence of an existing influence. Respiration rates and body temperatures show no departure from the normal in either sex.

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*Twenty women ranging from fifty to seventy-seven, with an agerage of sixty years, showed basal rates from —1 to +12 per cent, with an average of +5. A similar group of 29, the ages of whom lay between 50 and 78, with an average of 57, exhibited rates ranging from —1 to —12, the average in this case being —5. Unpublished data.—A. W. R.

In the last datum of the table, the alveolar carbon dioxide, a definite sex difference is found. Tensions in the male are entirely normal; in the female, on the other hand, there is a marked downward tendency which, in one-fourth of the series, produces levels ordinarily associated with acidosis. A like depression of CO_2 tensions in pregnancy was first recorded by Hasselbalch (41) and his findings were confirmed in detail by one of us (42). A possible import to this observation will be discussed later.

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*In such measurements all of the potential sources of error—barring only the gross mistake of spent soda lime or faulty gas analysis—operate to increase apparent oxygen consumption.

The last observation of the series here recorded deals with the carbohydrate tolerance. Prior to the establishment by one of us (43) of an intrinsic sex difference in the metabolism of galactose, but one record of a similar study was recorded in the literature. Artom (44) found that spayed bitches possessed an unchanged tolerance for invert sugar.* More recently, Tsubura (34) using glucose, has observed that castration of rabbits of both sexes lowered sugar tolerance. Estes and Burge (47), using paramecia, have demonstrated an increased sugar consumption by the organism under the stimulus of ovarian hormone. Burge and Williams (48) had previously noted a similar effect with insulin. In presenting the data here assembled, a word of explanation is necessary. As the entire matter has been discussed at length elsewhere (49), only brief explanatory notice is offered here. While the galactose tolerance of the male is totally uninfluenced by age or level of reproductive activity, the female tolerance is seemingly directly dependent upon the maturity and condition of the ovaries. Briefly, the prepubertal child gives a positive test with 20 grams; with the onset of the catamenia she advances to 30, and ultimately (usually within the year) to 40 grams, the normal level of the adult matured woman. With the menopause the tolerance level may remain at 40 or sink to 30 grams.† With a changing tolerance, the individual records of the tolerance dose in grams are insusceptible to collective reporting. By expressing changes in tolerance as percentage variations from the norm of the given individual, data are produced which possess a parity in their indications. Although the male tolerance is a constant, the same method of expression is adopted for the sake of uniformity. The data are given in Table VIII.

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*De Fellippi (45), quoting Quarta, recorded a result similar to the writer's with dogs, using glucose as the test sugar. Allen (46) denied the validity of these findings.

†It is not to be understood that abrupt transitions take place. The figures given are conditioned by the method of applying the test, which has been fully described elsewhere (50).

TABLE VIII

GALACTOSE TOLERANCE (1)

Observation		Unit	Male	Female
Tolerance Dose	High	Grams	30	30
	Low	Grams	30	20
% above normal		%	0	0
% equal normal		%	100	0
% below normal		%	0	100
Average Deviation from normal		%	±0	—44

1. The following cases are omitted from the tabulation as superimposed non-endocrine disturbances mask the gonad influence:

a. Two male castrates with tolerance at 40 gms. (+33%) had demonstrated late chronic interstitial nephritis.

b. Three aged females showing normal post-menopausal tolerance (30 gms.) had demonstrated severe chronic interstitial nephritis.

c. Four females, with tolerance averaging —80% below normal, were suffering severally from lesion of central nervous system (2), syphilis (1), and liver disorder (1). These conditions exercise a definite depressing influence on sugar tolerance.

The differences here exhibited are of the utmost diagnostic importance. Castration in the male is without influence on the galactose tolerance. Seemingly the testicle is not concerned with the regulation of the galactose metabolism. The effect on other sugars is at present unknown and is to be investigated. The omission of two male cases not recorded in the table is explained in the foot note.

Incidentally, the lessened permeability of the kidney, arising in an established nephritis, is a factor that should be considered in all forms of tolerance testing depending on urine findings. Unimpaired permeability should be demonstrated by test, and if there be indication of lowered kidney function, due allowance must be made in the interpretation of results.

Reverting to the table, we find that in every case lowered activity of the ovaries determine a lowered galactose tolerance. Further, in the castrates and severe functional failures, the level is at 20 grams. With the incipient or less severe functional cases the depression is less i. e. to 30 grams. It must be remembered that this series includes only females in whom the menstrual function has been established. What the effect would be of castration in prepubertal years is now a matter of conjecture, but from the data here and a number of unpublished observations, it seems probable that the prepubertal level of twenty grams would remain unaffected.

The striking point, from the standpoint of differential diagnosis, lies in fact, that while failure of the posterior lobe of the pituitary raises tolerance to a marked degree, and thyroid failure exercises either no influence or produces a slight increase, loss of function of the ovaries determines a decrease in tolerance to apparently a low limit of 20 grams. [The four cases which we have studied showing lower tolerances are already covered by the foot note (3) of the table.] The failure of the testicle to affect the galactose metabolism has only a less diagnostic significance, and indirectly bears upon other germane problems to be discussed later in this paper.

Before taking up the next portion of this paper, a word of explanation is necessary.

It will be noted in the foregoing discussion that but meager reference is made to the work of others. There is, of course, a most extensive literature bearing upon the subject in general, and ranging from the admirably careful, painstaking studies involving a wealth of experimental data, to those treatises designed to exploit some method of rejuvenation based upon manipulation of the organs of generation. Unfortunately for comparative purposes, a vast amount of this work deals with animal experiments that are inapplicable to the thesis in hand. A further hampering condition lies in the concentration on changing secondary sex characteristics as criteria of modified internal secretory activities. As these are certainly influenced by other agencies, at least in man (see discussion above), such observations, while striking and of the utmost import, bear but little relation to the work in hand. For example, so admirable a compilation as that of Lipschütz (4), collating a vast amount of original research with an equally exhaustive and selective canvass of the literature, contains no reference to the influence of the gonads on many important phases of metabolism. Again the emphasis laid upon the reproductive powers, which are certainly not solely intrinsic in internal secretory activity, obscures the issue.

Such pertinent observations as we have found in the literature have been incorporated in the running comment on the data reported by us. The meager tale of citations attests solely to the relatively slight consideration that has been given to this field of study.

PART II

Turning next to the clinical aspects of the condition, in reviewing the literature one is impressed with the lack of clear-cut definition of the hypogonad syndrome. It is true that a vast bibliography exists dealing with the influence on menstruation and on fertility. But there is missing, so far as the authors can ascertain, those graphic pictures so frequently presented in descriptions of many of the other endocrinopathies. There are, however, a few definite symptoms upon which observers are agreed, and these together with the more frequently considered features of the reproductive function will be considered in the light of our own findings. For obvious reasons, the two sexes will be discussed separately. The ovarian group has been augmented by a few later cases, and unless otherwise specified, the later statistics will derive from this larger series. The composition is given in the next table. Interesting members of the several groups will be discussed in detail later.

TABLE IX

Ovarian Group

Primary Ovarian Failure	200
Castrates (premenopausal) (1)	21
Castrates (postmenopausal)	2
X-Ray Sterilization	1
Female Pseudo-Hermaphrodites	2
Practical Amenorrhocics (2)	2
TOTAL	228

(1) Operated upon at an average age of 38 years.

(2) One of these, matured at 17, nearly 3 years later had had but 3 periods; the other matured at 14 and had had 4 periods in 11 years.

Practically all of the patients in the group were American born. No racial incidence was traceable in the very imperfect records available. The family history can best be presented in tabular form. The records are confined to immediate relatives. A number of the patients reported "nervousness" as a common familial trait. The term is an elastic one, and as applied to an immediate family may only reflect the patient's own nervous

TABLE X

Family History

Disease	Per Cent	
Cancer	20	
Diabetes	8	13
Other Endocrine	5	
Tuberculosis	23	
Insanity	11	

instability. The mental attitude of the patient with ovarian failure is touched on below.

A review of the chief complaints as offered by the patients themselves is most informative. In some cases, more than one disability was recorded as of basic importance, which explains the numerical discrepancy. Small groups without primary significance have been omitted.

TABLE XI

Chief Complaints (Patients')

Fatigue	72
Headache (1)	35
Mental and Nervous Disorders (2)	55
Convulsions	7
Gastro-Intestinal Disorders	20
Pain (1)	23
Menstrual Disorders (3)	28
Sterility (4)	6
Obesity	21
Vertigo	8
Deafness	20

(1) Not primarily associated with menstruation.

(2) Fourteen Psychoses with 5 attempted suicides, 11 Psychoneuroses, 30 Neuroses.

(3) See Table XV.

(4) See Table XVI.

Fatigue and weakness, cardinal symptoms in the other endocrinopathies, here characterize one-third of the entire group and as a secondary feature, they appear in the majority of the remaining cases. Headache is another important part of the clinical picture. Its dominance has already been noted in the pituitary and thyroid groups also. The number of established psychoses is interesting. A causal relationship here is still to be demonstrated; the observation, however, is possibly suggestive in the light of known mental deviations associated with physiological modifications of ovarian activity. Irritability and depression are frequently mentioned as features of a failing ovarian function. Record as to the first must depend almost exclusively on outside information, as the egocentric "hypogonad" usually lacks a philosophic objectivity in personal prospective. The authors have previously noted, however, the definite warrant for the inclusion of this sign as a most characteristic finding. Many of the patients name the second as a feature of their general condition.

In this connection a few words may not be inopposite on personality changes associated with depressed ovarian function. Comment has already been made of a similar condition in thyroid disease although the formula of its expression differs from that produced by ovarian failure.

An insistantly expressed egoism is the keynote of the hypogonad character. Coupled with, and dependent on, this is an active resentment toward a world that is but inadequately mindful of the patient's many excellencies. Hyper-emotionalism and self-pity are united with an attitude of acid criticism of environmental conditions that are always unsatisfactory. The psychological study of the average woman suffering from ovarian insufficiency would be a profitable though scarcely a pleasant task.

The cases presenting convulsions were practically all established cases of epilepsy. Again, a causal relationship remains to be established. Gastro-intestinal disorders are among the well recognized sequelae of ovarian failure. In this group, four patients had demonstrated gall bladder disease, and but very few failed in their histories to give some evidence of disorder of the alimentary tract. Constipation was an usual finding, 54 per cent recording it as a chronic state. Only five patients complained of diarrhoea.

Pain, as such, was offered by 10 per cent of the patients as a primary cause of disability. Localization was rarely specific, although the lower half of the trunk was usually included in the picture. In a few cases, at least, a very definite subjective element was demonstrable.

The cases presenting menstrual disorders and sterility will be touched upon later. Twenty-one patients offered obesity as a principal difficulty. As a matter of fact, 71 of the group were over 15 per cent above prediction and in many instances, far in excess of this modest level. On the other hand, an equal number were more than 10 per cent below their calculated weights (Dreyer) while the remaining 38 per cent fell within these reasonable limits. From these figures it is clear that ovarian failure certainly does not always determine obesity. Tandler and Grosz (14) have described a "tall" type but the emaciated group does not conform to this designation. In this connection, it seems to the writers possibly significant that with the pituitary there is the non-obese Lorain Levi type of failure; they have themselves described an underweight hypothyroid type; while in the ovarian group, as many are significantly under as are overweight. The underlying metabolic disturbances deriving from endocrine malfunction would seem to manifest themselves uniformly in a variety of ways.

In 8 of the cases, vertigo was a primary complaint, while a large number of the remainder gave it as one incident in the general disease picture. Hot flashes were by no means so common as might be inferred from the usual records in the literature. The majority, but not all, of the postmenopausal patients, both of natural and surgical origin, reported this symptoms, but it was conspicuously absent from the histories of a large part of the younger women. This would suggest, perhaps, that it is significant only in the more severe established cases and a sign of a marked hypofunctional level.

The age of onset and the duration of the chief complaint is potentially interesting. With many of the presenting symptoms, the onset was undoubtedly gradual and their first recognition coincident with some event which was, in many instances at least, unrelated to the underlying disorder.

The relatively large percentage reporting an onset during the years of adolescence and early childbearing is a possible point of interest though too great weight should not be placed upon it in view of the uncertain character of the data from which it derives. A second feature in the table is the upward progress of the duration until the menopausal age, at which

TABLE XII

Onset and Duration of Chief Complaint
(200 Consecutive Cases)

Interval	*Age of Onset*	*Average Duration*
From birth	6.0%	26 years
0-10 years	3.3%	
11-20 years	32.0%	3 years
21-30 years	31.3%	6 years
31-40 years	16.0%	9 years
41-50 years	6.7%	13 years
51-60 years	2.7%	11 years
61-70 years	2.0%	12 years

time it apparently becomes stationary. This too may be an artefactual relationship; it is recorded only as a statistic.

The incidence of the more common infections as derived from the history has been reduced to tabular form. The relative frequencies would seem to indicate a definite degree of susceptibility to the commoner complaints.

TABLE XIII

Incidence of Earlier Infection

Disease	*Per Cent*
Measles	86
Whooping Cough	61
Mumps	50
Chicken-pox	49
Influenza	30
Scarlet Fever	22
Pneumonia	12
Diphtheria	11
Rheumatic Fever	10
Typhoid	9

Yet another datum is found in the record of previous surgical manipulation of the pelvic organs. As already noted (Table IX), there were 23 castrates in the series of 228 consecutive cases. In addition to these were the following: (See Table XIV.)

In other words, including the castrates, one woman in every four had had at least one laparotomy (several reported as many as four or five) for surgical manipulation of the pelvic organs, and 7 per cent more had been curetted for reasons unassociated with any of the incidents of pregnancy. Several of such matters will be discussed at length in a later paper.

TABLE XIV

Laparotomy for	
Unilateral oöphorectomy	14
Resection of ovarian cysts	5
Resection of uterine fibroids	2
Uterine abscess	2
Uterine suspension	12
Therapeutic curettage (excluding miscarriage)	16

The importance of a thorough physical examination has been stressed throughout these papers. A few of the more significant observations may next be recorded.

The prevalence of skin eruptions is one usual finding that our records do not entirely confirm. Acne was common, it is true, but this mild inflammatory condition is associated with too many other disease states for it to assume any specific meaning here. But three of the entire group recorded skin eruptions as major complaints, two with eczema and one with psoriasis. Vulval pruritis is usually considered to be a frequent manifestation and this is scarcely to be wondered at, in the light of the frequent incidence of glycosuria. Two of our cases presented this condition as a complaint and a number of others recorded earlier attacks.

In view of the frequent allocation of hypertrichosis to adrenal disease, our own figures are of more than passing interest. Unfortunately, no record of pilosity was made in some of the earlier cases. In 134, however, in which complete observations are reported, 62 or 46 per cent showed marked hypertrichosis and of these, 45 had a definite male configuration of the pubic hair. As already noted, Falta's cited cases of adrenal disease with virilism all showed a concommitant ovarian involvement whenever record was made. The authors do not feel that their own observations settle the question; they record only a number of cases presenting excessive pilosity with retrogression of certain secondary sex characteristics, in which no evidence of an adrenal complicity was demonstrable. True, the pluriglandular enthusiast might adduce this observation to support his thesis. but the hypernephromata associated with virilism are commonly interpreted to indicate adrenal overfunction, a condition that would ill accord with many of the laboratory findings in this series. Further, if pubertas praecox derive in many cases from adrenal overfunction, one faces again an antithetical and contradictory series of facts which cannot be explained away.

Nearly 10 per cent of the cases presented deafness as a chief complaint. As one of the author's associates has shown [Drury (51)] endocrine failure may be a factor in otosclerosis, and a number of these patients were referred for study on that basis. A fraction of them proved to be true otosclerotics, but the remainder demonstrated defects of infectious origin, establishing a purely non-endocrine etiology for the deafness.

That the calcium metabolism is influenced by the level of ovarian function is generally conceded although the mechanism must be regarded as wholly unknown.

One-third of the entire series showed evidence of past or present gravely defective teeth, while an additional 12 per cent were reported with the teeth in "fair condition" only. The cross section of the social background of the group precludes neglect as the primary causal agent.

Diseased tonsils have already been noted as of very frequent occurrence in pituitary and thyroid disease. The present group offers no exception to the previous record. Forty-four per cent of these patients had had one or more tonsillectomies, while the laryngological examination showed an additional 24 per cent with definite tonsillar infection. The total of 68 per cent compares favorably with the incidence of all of the commoner infections with the exception of measles. Whether a disturbed metabolism of endocrine origin predisposes to a lowered resistance to infection or focal infections influence selectively the level of endocrine function, is a question for the future to settle. The high coincidence in the conditions discussed would seem to indicate a possible inter-relationship.

A number of the patients (15 per cent) showed some thyroid enlargement, in fact several of these were referred as probable thyroid cases. In no case was the enlargement marked and equally, in none of them was thyroid disease demonstrable.

Residence in so-called goiter districts, the sequelae of child bearing and similar agencies, were apparently responsible for the occurrence of these non-toxic goiters.

The routine heart examination developed reportable abnormality in 20 per cent but grave cardiac conditions were rare. As previously noted, 10 per cent of the group had had rheumatic fever. Similarly, while 16 per cent gave evidence of past or present pulmonary disease, a number of patients with a history of asthma or hay-fever and a few cases of healed tuberculosis accounted for practically all of them. In no case was there any apparent relationship between any chest condition and the presenting endocrine disease.

A general tenderness on deep palpation of the abdomen was reported by 11 per cent of the group. In view of the surgical histories recorded, added to the subjective attitude of many of the patients, the number is small. The gall bladder cases all showed tenderness in that area, but with the others, the definition was usually vague.

Diminished or exaggerated reflexes were exhibited by one in three, but beyond these and one doubtful Babinski, the routine neurological examinations were not remarkable.

Turning now to a consideration of the exocrine functions (in the regulation of which, in the last analysis, endocrine activities may be implicit), the age of the establishment of the catamenia invites attention. The accompanying graph (Graph I) gives the records of 197 cases in this series. One child maturing at 7 and the two pseudo-hermaphrodites are not included. Seventy-five percent fall within the conventional 12 to 14 year limits, while over half (28) of the remainder impinge upon the chronological limits of the restricted group. Ten per cent only, show a definitely retarded maturity; two of the patients are in the group later castrated, a rigorously just proportion. If the figures obtained are meaningful, ovarian failure would seem to be either an incident of the years of maturity or, if a prepubertal existence be assumed, without signal influence on the fact of maturation. One child had a unilateral oöphorectomy at 12 and menstruated at 13. The others were operated upon much later and after maturing. The subsequent menstrual histories are presented in tabular form.

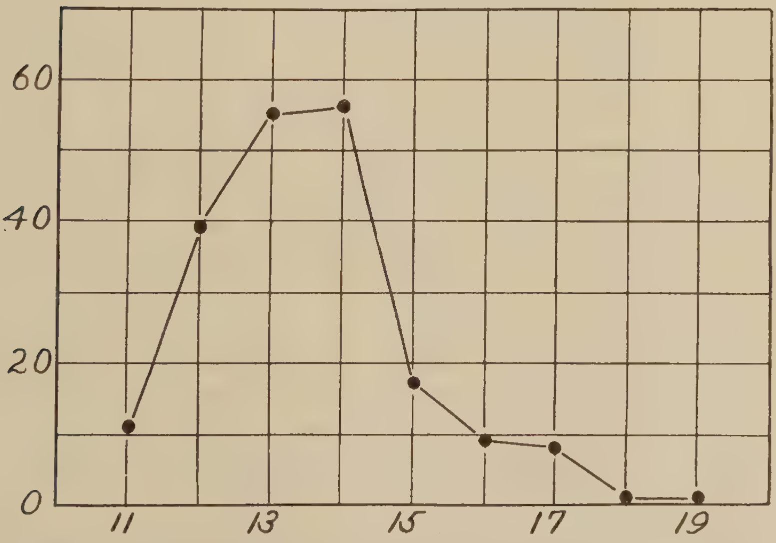
TABLE XV

MENSTRUATION (214 CASES)

Period	Diminished	Normal	Increased
	—Amount of Flow—		
Irregular (39%)			
Increased	14	36	13
Decreased	3	5	9
Both	1	0	3
Total	18	41	25
Regular (61%)	23	83	24
Total	41	124	49
	19%	58%	23%

Regularity and amount of flow are the two variable elements considered. In view of the frequent statement that ovarian failure presupposes a disturbed menstrual function, these figures are enlightening. Nearly two-thirds of the group record a normal rythmic incidence of the function, and a slightly smaller number present a normal flow. Eighty-three (39 per cent) are both regular in rythm and normal in amount. Another usual statement that ovarian failure shortens the interval is far from substantiated by these records. Of the irregular

PLATE I



Maturity curve. Number maturing at each year. Omits one child menstruating at seven years, and two female pseudohermaphrodites who never menstruated.

group, only 17 show an accelerated recurrence, while nearly four times that number have delayed periods. If one considers the absolute incidence of shortened interspace in the entire series, the percentage shrinks to wholly unconvincing proportions. Four patients, only, show that double irregularity which is so common a feature of thyroid failure. Avoiding dogmatism, it may be said that in this series, ovarian failure has a tendency to lengthen the menstrual interspace in that smaller proportion which depart from the conventional rythm.

One very striking fact may be commented on in passing. In Table X, only 28 of the patients offered menstrual disorder as a chief complaint, although 84 report irregularity of the function and 24 an increased flow. Even more significant is the fact that 136 of the group reported dysmenorrhoea of varying degrees of severity. The disproportion between the actual incidence and its presentation as a disability emphasizes the pathetic acceptance of painful menstruation by the average woman as a normal complement of the exercise of this particular physiological function.

It will be remembered that six of the patients offered sterility as the cause of presentation for study. The fertility data are interesting in this connection. It should be stated that, of the augmented group, 121 were unmarried (53 per cent) and the remainder had had one or more matrimonial experiences. The relative equality of the two groups may bear on the elimination of sexual inactivity as a predisposing cause to gonad failure. In the writer's opinion, the series is too restricted to indicate more than a possible trend. The fertility data are given in Table XVI.

TABLE XVI

FECUNDITY (100 CASES)

Group	I	II	III	IV
Miscarriages	0	A = 2	0	Av. = 2(1)
Children	0	0	Av. = 2	Av. = 3
Number	31	10	34	25
Duration of Marriage—				
Longest	32 years	21 years	30 years	28 years
Shortest	1 year	2 years	3 years	2 years
Number < 5 years	13	4	2	1
Total Average	8 + years	11 + years	13 + years	18 years

(1) Omitting 1 case with 24 miscarriages. See text.

Four permutations are possible as exemplified in the four groups. In all the cases recorded, contraception was specifically denied. When this has been practised the degree of fecundity in the non-pregnant naturally remains a matter of conjecture. For obvious reasons induced abortions are likewise omitted.

Nearly one-third have never been pregnant, while 10 per cent more have conceived but have been unable to complete their pregnancies. While lues cannot be ruled out absolutely in any case, all of the patients presented here, with but two exceptions, had negative Wassermans and, in many cases, negative Kahn tests as well. The two exceptions fall in Group IV, having borne children as well as having had miscarriages.

Forty-one per cent of these patients were sterile at the time of study and, even if these subjects be deducted who had been married less than five years, the remainder (24 per cent) falls notably above the average percentage of infertility as recorded by others. Reynolds and Macomber (52) conclude that from 10 to 12 per cent represents a fair measure of infertility and in this estimate they are unable to eliminate those arising from contraception. On this basis the present figures show an augmented degree of infertility of striking proportions. One-third of the group have completed all of their pregnancies successfully and one-fourth have conceived several times with average result of 60 per cent productivity. As noted above, one case is omitted from the computation of the miscarriages since, after bearing one child, she subsequently had 24 incomplete pregnancies, the husband being luetic. The point of note in this case is the very high initial fertility of the couple which, in spite of all handicaps, permitted 25 impregnations. The patient's weary tale was ended by a panhysterectomy several years before entering the clinic. At no time did she give any evidence of specific disease and at the time of her study the serological tests were uniformly negative.

As was stated in the first paper of this series and reiterated in the later discussions, the various special examinations serve the primary purpose of determining the presence or absence of a non-endocrine disorder to which the patients disabilities may be referred. Only exceptionally, and this is peculiarly true of the present group, do they add positve evidence of an endocrine involvement. A brief partial analysis of 100 selected cases in which a total of 574 special examinations* were performed, may be considered.

Eye: Of a total of 90 examinations, 72 gave positive findings. Enlarged blind spots were found in 46, while patients with disc defects such as tallow color, indistinct margins, etc., were 24 in number. Twenty-two showed contracted fields, of which 6 demonstrated a symmetrical contraction of marked degree. Stiff pupils were found in four cases, and two showed the so-called "snuff fundi" usually regarded as a sign of congenital syphilis. Two scotomata were delineated and one case a recognized atrophy of unknown cause.

Ear: Of 20 ear examinations, 7 showed infective processes and the remainder defined otosclerosis. One-third of 18 Barany tests gave positive evidence of labyrinthine disease. Fourteen of 22 audiograms showed marked loss of aural acuity and the remainder indicated only a lesser degree of impairment.

Neuro-psychiatric: Examinations were made of 63 of the series. The results can be presented in tabular form.

TABLE XVII

Neuro-psychiatric Diagnoses

Psychoses	9
Psychoneuroses	6
Neurasthenia	11
Hysteria	2
Epilepsy	6
Organic disease	7
Chorea	2

The seeming discrepancy between these figures and certain of those recorded in Table XI is due to the fact that a number of the patients were referred from institutions where the nervous and mental elements had already been evaluated.

Radiography: Ten patients showed small, shallow or otherwise remarkable sellae. None of them gave evidence of pituitary tumor. The impossibility of delimiting the normality of the sella shape has already been noted (53). Sinus involvement was found in 14 of the cases studied. A past or present pulmonary disease was demonstrated in 13 patients; six of these showed a protein sensitivity. Seven gave x-ray evidence of cardiac enlargement, confirming the number demonstrated by the electrocardiograph. Eight out of 13 gastro-intestinal series showed disease, chiefly in the appendix, while one Graham test (intravenous) was positive in five performed.

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*The average for the entire series is slightly less than three per person. In many instances "Short Form" subjects fail, for a variety of reasons, to return for all of the special tests requested. Averages in later series, however, are much higher, i. e., "Long Form" 8+, "Short Form" 5+.

Pelvic: Of the 55 cases examined, 13 gave evidence of some disorder, chiefly in the uterus. One infantile and one juvenile organ were found; the others were chiefly fibroid tumors.

Of the numerous other examinations, none gave data of sufficient interest to warrant comment. It will be noted from the above that none of the findings were especially pertinent to the positive determination of endocrine disease. Even the eye results, although they indicate a large degree of metabolic disturbance, fall short on any specific endocrine indication, in this group.

Limited as are the clinical indications, outside of the functions intrinsic in reproduction, which are regarded as characteristic of ovarian failure, the complementary testicular picture is even more circumscribed in detail. The study in adult years of males castrated in childhood offers some help, it is true, in defining characteristics of what may be designated as early eunuchoids. But without more objective methods of analysis than have been applied to this problem, there is always the unresolved question with the latter group if the observed genital arrest is more than one secondary evidence of early pituitary or thyroid disease—resultant and not causal. Studies of adult castrates whose glandular ablation has occurred after maturity has been established are extremely rare in the literature. Falta (21) comments on this and, in spite of the wealth of clinical material at his command, is constrained to present as his illustrative case an individual who contracted gonorrhoea with bilateral orchitis and, later, lues before tuberculosis necessitated a bilateral orchidectomy which lessened but did not obliterate his libido et potentia coeundi at the age of 26. In his 37th year he had a goiter which later spontaneously receded, and Falta saw him seemingly when 49 years of age. Falta comments on the disturbing elements, but states that the patient recorded his modified habitus as first appearing after the operation.

The overgrowth of the long bones due to retarded epiphyseal closure, the lowered sitting height index arising from this cause, and a gradual assumption of an outward female habitus with modified pelvic contour are primarily referable to failure in youth. Even so, Tandler and Grosz (14) recognized both a fat and a tall type, although they state that the latter manifest a tendency toward characteristic fat desposition.

The four eunuchoid cases in this group show respectively sitting height indices of 0.514, 0.520, 0.525 and 0.550—in other words, one only, the 10-year-old child exhibits a significantly low value, while another is markedly above the normal average.

A loss of body hair with a feminization of the pubic contour is not confined to malfunction of the testicles, as numerous pituitary studies have shown. A wrinkled skin and some pigmentation are other features recorded, but in the main, there is a notable dearth of informative and suggestive detail. That this should be the case is in no small measure implicit in our findings. As has been emphasized repeatedly in these papers, male castration in adult years produces but minor changes in functional levels as ascertained by objective methods. In the main, the physical picture of the adult castrate presents a definite and general normality. The present small group is composed of men castrated in adult years (3), of cases of bilateral orchitis as a sequel to mumps in the years following puberty (4), and boys and young men exhibiting a marked arrest of sex development (4) in whom no evidence of pituitary or thyroid disease could be demonstrated by careful and detailed study.

With so small a group and one so divergent in the several elements that compose it, a statistical analysis is meaningless. A few comparisons may be drawn with certain of the more significant findings in the ovarian group. Five of the eleven gave fatigability as their chief complaint, and the majority of the remainder reported it as an important secondary symptom. Four were referred for genital underdevelopment, and two for sterility. Of the eight adults but three were married, and all were sterile save the aged man whose orchidectomies had been performed in the preceeding two years. One of the castrates subsequently married and was able to have intercourse with his wife to her satisfaction (see case B-42 in next section). Diseased tonsils were again prominent, five having had them removed, while four others showed infection. Three of the four eunuchoids (10, 13 and 16 years) were of an obese feminine physical habitus, the remaining patient being spare but with somewhat broad pelvis. Body hair was usually scanty although this feature, as one might anticipate, was less marked in the castrates and post-orchitics. Constipation was an almost uniform finding, even more markedly than in the female group. The other findings lack a sufficient degree of concordance to be significant.

In the next section, typical case protocols from each of these groups will be given and will serve to elaborate the thesis presented above.

PART III

CASE PROTOCOLS

To complete the paper, the authors desire to present a few of the cases in detail. In reviewing them, the reader is reminded that many of the factors contributing to the diagnosis could not be included here. Emphasis will be laid upon those points which may be correlated with the matters which have been discussed in the earlier pages.

GROUP I. GENITAL ANOMALIES.

CASE B-21. PSEUDOHERMAPHRODITE. The patient's chief complaint was of obesity from which she stated she had suffered since early childhood. The history which we obtained was very limited and as events transpired not entirely ingenuous. During the course of the study several anomalies in the laboratory picture developed, and as a result one of us questioned the patient much more searchingly in regard to her history. She then acknowledged that she had never menstruated and was what was called an "hermaphrodite." She had been cognizant of this condition since early childhood but her family, for religious reasons, had refused to allow any physical examination and in the few years that had elapsed since their death the earlier inhibition had persisted.

Family History: Was entirely devoid of significant information.

Past History: The patient reported minor ailments and, later, the information given above.

Physical Examination: The patient was markedly obese, the hair soft and abundant, the thyroid not enlarged; the breasts were moderate in size and essentially feminine in contour. There was reported a slight cardiac murmur at the apex which was later denied. There was abundant pubic hair with a tendency to male configuration, marked pilosity on the legs and a slight mustache. Routine neurological findings were normal.

Laboratory Summary: The patient was 33 per cent overweight; a basal rate of —11 per cent was recorded, and this was probably somewhat above the truth; blood pressure was low. Alveolar CO_2 was a low normal. The residual nitrogen fraction of the urine showed an upward tendency. Galactose tolerance was half the normal for a woman of the patient's age. The urea curve was normal. The blood morphology showed a substantially normal picture.

Radiographic findings of the skull and sella were normal.

Pelvic examination disclosed a congenital absence of the vagina and a prominent clitoris 1½ cm. in diameter.

Discussion: The general picture presented was that of ovarian failure. Because of the patient's obesity and the other impediments it was impossible to demonstrate the ovaries. One interesting fact

TABLE XVIII

	Genital Anomalies				Homosexual	
	1	2	3		4	5
Case Number	B-21	B-946	B-812	B-1008	B-408	B-530
Sex	F	F	M	M	F	F
Age (yrs.)	34	4.5	4.5	5.0	36	19
Height (cm.)	166	120.5	129.5	137.4	164	169
Weight (kgm.)	83.5	23.2	28.8	33.2	43.6	79.2
Weight Deviation (%)	+33	−19	−19	−22	−29	+23
Lung Volume Deviation (%)	—	−2	−48	+3	−27	−4
Basal Rate Deviation (%)	−11	875 cal.?	1058 cal ?	1260 cal.?	−13	+5
Blood Pressure (mm.)	110/78	96/50	96/58	104/56	102/62	110/62
Pulse Rate (per min.)	66	88	70	86	76	71
Temperature (deg. F.)	98.0	98.0	98.2	98.8	97.9	99.0
Alveolar CO_2 (mm.)	39	43	42	38	31	38
Urine Volume (cc.)	1440	380	530	1120	440	1420
Spec. Grav	1.015	1.028	1.024	1.015	1.029	1.020
Albumin	0	+	0	+	0	0
Casts	0	0	0	+	0	0
Sugar	0	0	0	0	0	0
Total Nitrogen (gms.)	10.73	5.37	6.35	8.11	0	0
Residual Nitrogen (%)	8.4	10.9	16.0	10.7	5.42	11.74
Phen. Sulph. Phthal (%)	72	63	65	60	5.8	5.4
Galac. Tol.—					64	49
Normal (gms.)	40	20	30	30	40	40
Observed (gms.)	20	20	10	20	20	20
Deviation (%)	−50	+0	−67	−33	−50	−50
Blood—						
Non-Protein Nitrogen (mgm.)	27	32	32	30	32	32
Uric Acid (mgm.)	3.5	3.8	3.2	3.5	2.2	3.3
Sugar (mgm.)	98	100	75	83	87	86
Haemoglobin (%)	100	85	98	95	90	90
Erythrocytes (10^6)	5.76	4.11	6.63	5.32	4.39	4.51
Leucocytes (10^3)	10.40	8.55	8.50	12.45	8.00	5.70
Neutrophiles (%)	68	47	55	56	32	55
Lymphocytes (%)	29	44	31	30	63	38
Eosinophiles (%)	2	3	0	2	1	2
Monocytes (%)	1	6	14	12	4	5
Misc. (%)	0	0	0	0	0	0

1. Pseudo-hermaphrodite (female).
2. Pseudo-hermaphrodite and Pubertas Præcox (female).
3. Pubertas Præcox (male).
4. Homosexual (male).
5. Homosexual (female).

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*Observed heat production (see below).

given by the patient was that for many years she had had a headache which would last about one day, and which came at four-week intervals. During the day of the headache she had frequently noted that her perspiration had a peculiar and somewhat offensive odor. From the fact that the secondary sex characteristics had developed, it seems fair to assume that the patient presented a genital inadequacy, and that some ovarian tissue was present. Another point worthy of note was that her sitting height index was practically normal, the long legs of the so-called eunuchoid being absent. A surgical opinion was requested and it was decided that there would be no real advantage to the patient through surgical interference.

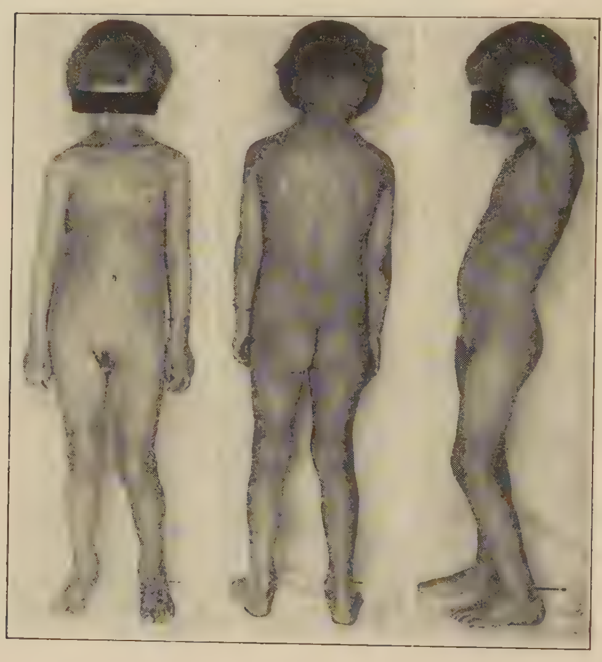
CASE B-946. PSEUDOHERMAPHRODITE WITH PUBERTAS PRAECOX. This little patient was a child four years and seven months of age who was first seen in the Out-Patient Department. The family physician had referred her for an investigation of a definite genital anomaly. The child had a hypertrophied clitoris resembling the penis of a boy of 12. In addition there was a definite growth of pubic hair although the breasts were still rudimentary. Outside of the genital condition the child was in perfect health. The study was undertaken to resolve the sex of the patient and equally to ascertain the cause of the precocious puberty.

Family History: The father, mother, and one older sister are living and well and present no anomalies. A second child, a male, born before the patient, cut his first tooth at eleven months, talked at twelve months, walked at sixteen months, and weighed 40 lbs. at the time of his death from meningitis shortly before his second birthday. The patient's genital anomaly was recognized when she was but a few days old. The family physician, however, most judiciously advised delay in attempting any modification.

Past History: The patient weighed 10 lbs. at birth, cut her first tooth at eight months, talked at twelve months, and walked at eighteen months. She had pertussis at 2½, discharging ears for about a fortnight at eighteen months, but had otherwise been a strong, active, healthy child.

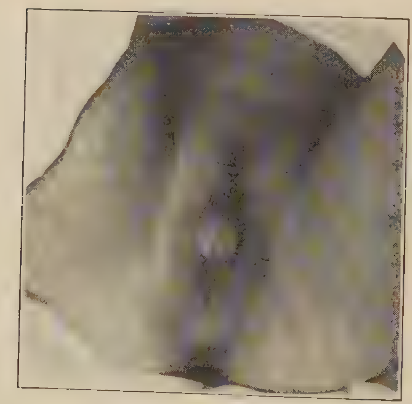
Physical Examination: The patient was a well developed, somewhat undernourished child between four and five with abundant hair on the head; a suggestion of slight exophthalmos was noted, but other observation demonstrated that this was a familial characteristic. Her ten upper and ten lower teeth were in fair condition. The tonsils were large and cryptic. The voice was somewhat deep and the speech slightly thick. A single pea-sized gland was felt in the upper right anterior cervical chain. It was not tender. The breasts were undeveloped and the nipples suggested the male type. The heart, lungs, and abdomen were normal. There was a considerable amount of brown pubic hair extended from the upper border of the symphysis, separating on either side of the hypertrophied clitoris. This latter was 4 cm. long, 1.3 cm. in diameter, and suggested a penis and glans after circumcision. There was no evidence of any orifice. The whole structure curved downward over an opening immediately beneath it about 1 cm. in diameter. At the upper edge of the apparent vaginal orifice could be seen the urethral opening. The vaginal slit was overhung by folds of hair-covered skin resembling labia majora. There was no evidence of scrotum, testicles, or patent inguinal canals. During the examination the clitoris became erectile. There was no axillary hair or other abnormal pilosity. The patient's gait on walking was noted to be a little clumsy.

Plate II



Case B-946

Plate III



Case B-946

Laboratory Summary: The child was distinctly tall for her age, 19 per cent under her predicted weight, and with normal lung volume. The basal rate was determined by a series of observations as 875 calories. Comparison with the age standard, which would be obviously unfair, gave her a value of +17 per cent. With the area, height and weight standards of Benedict-Talbot (54), the observed and predicted practically coincided. By the Harris-Benedict (24) standards and the Bailey (55) area computation, she was about 20 per cent below prediction. It may be safely said that the child did not present a high basal rate and it was our feeling that the rate was probably slightly though scarcely significantly low. The blood pressure was low, the pulse slightly rapid. CO_2 was normal. The several urines showed a very scanty volume with good elimination in relation to the patient's weight. Albumin was constantly observed. The average protein intake was somewhat low, the residual nitrogen fraction high. She reacted positively with 20 grams of galactose, negatively with 10. This would be normal value for a female child in the prepubertal period and a depressed tolerance for a boy of the same age. The blood uric acid was relatively high. The blood was lymphoid in type, showed a 3 per cent eosinophilia, and a slight secondary anaemia.

Audiogram: Showed substantially normal hearing.

Ear Examination: The ear drums were markedly thickened.

Barany: Normal reactions were obtained.

Nose and Throat Examination: The tonsils were enlarged but not demonstrably offending.

Chest Examination: The findings were normal.

Neurological Examination: The examiner regarded the patient's gait as normal and found no evidence of organic nerve lesion.

Pelvic Examination confirmed the statement given above, and noted that the labia were rather rudimentary and defined the existence of a vagina. No internal genitalia could be palpated, which would be explained by the patient's youth.

Radiography: The skull showed a persistence of the frontal suture and convolution impressions on the inner table. The sella and sinuses were normal. The chest was normal.

Cardiogram: Normal findings were obtained.

Eye Examination: The patient was too young to permit delineation of the visual fields. The fundi showed snuff pigmentation throughout.

Urea Index: A normal value of 155 was obtained.

Lumbar Puncture: This was felt necessary in view of the eye report. The pressure was 18 cm., rose to 26 cm. on pressure, returned to 18 cm. with removal of pressure. When 15 cc. of fluid was removed the pressure fell to 12 cm.

Spinal Fluid was strictly normal.

Discussion: At this point there were two definite problems to be considered. First, the sex of the child, in order that the interpretation of the various laboratory data might be as exact as possible. There was, further, the important social problem which could become acute in the course of a few years. The second question was the basis of the patient's precocity. Three endocrine factors come certainly into question, with possibly a fourth. Over-activity of the gonad, pituitary overproduction, and tumor of the adrenal cortex have all been recorded as causative agents. While the case for the first is less well sustained and would probably imply tumor growth, it can not be ignored. The fourth possibility is, of course, the pineal, but here the evidence is even more doubtful. If the child had a cortical tumor, surgical intervention was essential, and as they are usually malignant the time factor had to be reckoned with. Further, exploratory laparotomy would aid in the resolution of the child's sex as well as make possible removal of an adrenal tumor if one were found. On this basis permission for laparotomy was requested from the parents and was granted. The child was operated upon by Dr. T. E. Chandler, to whom we express our sincere thanks. We quote directly from Dr. Chandler's report:

> *May 10, 1928:* "This operation was made for the purpose of determining the sex of the child, and also with the idea of locating, if possible, the cause of her condition. Incision was made in the median line of the abdomen. Exploration was first made of the kidneys and no departure from the normal was found in either kidney. The pelvic parts were then examined. In the median line, extending upward from what seemed to be a normal sized cervix, was a cord about ½ cm. in diameter and enlarging to 1 cm. in diameter, about 2.5 cm. in length. It was flattened anteroposteriorly and was not more than ½ cm. in thickness. This was evidently a rudimentary fundus uteri. Springing from the cornua are normal tubes such as would be found in a girl of about her size with ovaries normal for her apparent age. Exploration was made of the canal of Nuck; no evidence of testicles was found here or in the labia. The wound was closed with layer sutures of catgut and stay sutures of silk worm gut.
>
> "*May 19, 1928:* The sex of the child having been determined as that of a girl, with the consent of the parents an enlarged clitoris was removed. A circular incision was made about its base which was dissected up from attachments and the wound closed with sutures of catgut."

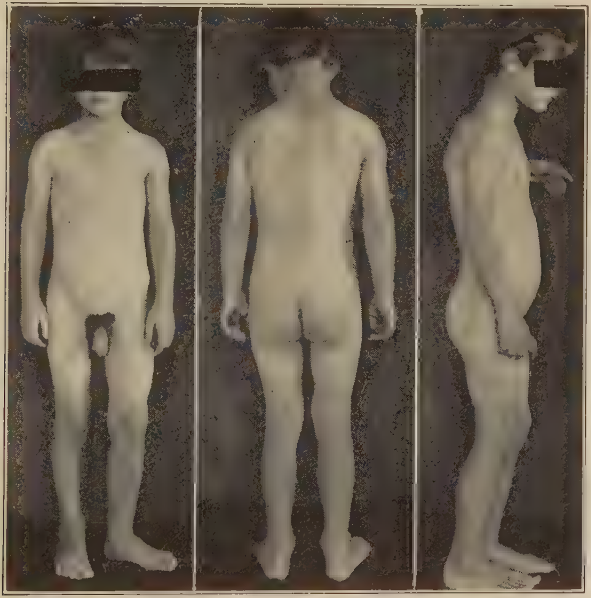
The determination of the child's sex as female eliminated one uncertainty in the interpretation of the data. At the present time we feel that hypergonadism and, equally, cortical tumor can be eliminated from the picture. The remaining condition, pituitary involvement, is not clearly defined although offering some supporting evidence. The more remote possibility, a pineal involvement, is also to be held in consideration. On the basis of probability the child has pituitary involvement. She will be studied at frequent intervals in the hope of resolving the matter within a reasonable period of time. Through the courtesy of the mother we were able to make a rather complete study of her. Elaborate analysis is omitted in the interest of economy of space. The general picture was one of normality, exhibiting solely an essential hypertension. Pelvic findings were devoid of features germane to the present matter. The serological findings, as well as the remaining picture, were normal.

Case B-812 and B-1008. Pubertas Praecox. The case of this patient is reported as in some ways it parallels that of the preceding patient, although no doubt as to the sex existed. The patient was a 4½-year-old boy with stature of a lad of nine, strong, muscular and vigorous, with large genitalia, well-grown pubic hair and other evidences of maturity. As his early puberty was of possible endocrine origin, he was submitted for the study to ascertain if possible its cause.

Family History: The patient is the second child of five, born in an interval of six years, to parents who were, respectively, 21 and 19 at the time of the patient's birth. At the time of the patient's admission the mother, at the age of 22, was far along in her sixth pregnancy. The other children and the father and mother are entirely normal and nothing which bore on the case could be elicited concerning the grandparents.

Past History: While the mother was on her way to the hospital to be confined she met with an accident, but sustained no serious injury. The delivery was normal but delayed. The boy's first tooth appeared in the seventh month, he walked in the fifteenth, and talked at two years of age. He had whooping cough and chicken-pox. The history was otherwise not relevant. His large size and unusual genital development were first noticed at the age of one. As he has grown he developed a number of behavior problems which led to his reference to the Fernald School. Through the courtesy of Dr. Ransom Greene, to whom we express our sincere thanks, his records have been made available. His school comment on social history is: "Egotistical, quarrelsome, selfish, stubborn, seclusive, somewhat resentful of authority, a leader, difficult to control. Shows no affection for mother. Teases other children." His moral reactions: "Steals and hides things. Masturbates. Started fire in a tin pan. Developing delinquent tendencies." At the time of his first contact with the Fernald School his intelligence quotient was 93.

PLATE IV

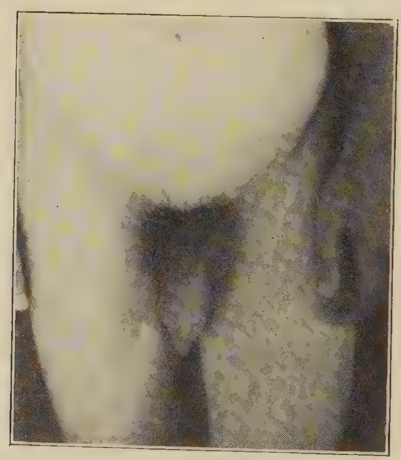


Case B-812

Physical Examination: The boy had the appearance of a well-developed and nourished lad of nine, of strong, sturdy build, the knee and ankle joints being especially large. The voice was of deep, male type, the genitalia of adult size and development with some pubic hair. Fine, light hair covered the face, neck and arms; that of the head was thick, light and fine. There was a small amount of discharge in the nasal cavities. Twenty first teeth were present, those in front being widely spaced; several large cavities were noted. The tonsils were large, the thyroid was not palpable. The pulse rate was somewhat rapid, and there was a slight systolic murmur at the apex. Examination of the abdomen was somewhat unsatisfactory. The penis was 9 cm. long in a relaxed state; scrotum and testicles were of proportionate size. There was a slight tendency to spasticity in the legs, most noticeable in the adductor muscles, producing a peculiar type of gait. At times the patient experienced difficulty in voluntary separation of the legs. The routine neurological examination gave substantially normal findings.

Laboratory Summary: The boy was, by normal calculations, 19 per cent underweight, which is actually not the case, as his sitting height index was very high (.57); his lung capacity was about half that of prediction. The standards for the basal rate at this age are not well defined. His observed rate in the best of a series of observations was 1058 calories. An independent measurement by Dr. Fritz B. Talbot, to whom the authors express their indebtedness, gave a value of 1145. Neither of these rates was probably quite basal. Comparison with the various standards show a range of from +39 per cent by the age standard to —22 per cent by Bailey's area standard. The several Talbot values are slightly higher than the lowest observed rate. The age value is patently meaningless and we felt in this case as in the one just discussed that the rate was either normal or slightly depressed. The blood pressure was low, urine volume low, protein intake slightly low, residual nitrogen fraction definitely high. The sugar tolerance was much depressed, the blood sugar slightly below the conventional normal. The blood morphology showed a slightly high red count and an increase in the endothelial leucocytes. A long series of blood pressure measurements showed an average of 96 systolic and 55 diastolic.

PLATE V



Case B-812

Radiography: The frontals and sphenoids were undeveloped; the sella was small with thick posterior clinoids. Hands, wrists and knees show the development of a 12-year-old boy. The mediastinal shadow was slightly enlarged. A gastro-intestinal series was entirely normal. At one of the earlier examinations it was thought that a mass could be demonstrated in the neighborhood of the right kidney. This was not confirmed by later examinations, but it was felt that the matter should be thoroughly investigated and a pyelogram of the right kidney was taken which gave entirely negative results.

Cystoscopy gave normal findings.

Bilateral Ureteral Catheterization: Normal function was demonstrated in both kidneys.

Chest Examination gave normal findings.

Orthopedic Examination: The examiner found evidence of beading at the costochondral sutures, suggesting an earlier possible rachitic condition.

Nose and Throat Examination: The tonsils were found to be hypertrophied and infected.

Neurological Examination gave normal findings.

Abdominal findings were normal.

Eye Examination: Owing to the patient's age the fields could not be demonstrated. Enlarged blind spots were detected by use of the Lloyd slate. Remaining findings were normal.

Urea Index: Value of 72, which implies a loss of permeability,

Discussion: This case, like the one previously discussed, gave evidence of a precocious puberty, the primary cause of which could not be completely ascertained by the study as given. The patient's low blood sugar, which was confirmed by several observations, and the consistently low blood pressure were suggestive of lowered adrenal function in which presumably the medulla would be primarily involved. On the other hand, the various genitourinary examinations argued against a cortical tumor of any magnitude. The lowered sugar tolerance, as has been shown by one of us, would be entirely consistent with an adrenal insufficiency. The mediastinal shadow could be interpreted in several ways, among which could be a persistent thymus. With the very dubious case for an endocrine activity of this gland it was felt unnecessary to consider this possibility as of primary significance. If there were an adrenal tumor its prompt removal was essential. On this basis permission for an exploratory laparotomy was received from the parents. The patient was operated upon by Dr. R. C. Wiggin, to whom the authors express their indebtedness. We quote:

> "Under ether, operation was performed by making incision in the right semilunaris opening into the abdominal cavity. The intestines were pulled to one side and both kidneys palpated. There was no evidence whatsoever of tumor in either kidney, but I incised the posterior peritoneum and freed the kidney and examined the adrenal region on both sides. No disease was found. The peritoneum was then closed and a large appendix was removed by the cuff method. The wound was closed with catgut and silk worm gut."

With the adrenals probably eliminated, no evidence of testicular involvement, and the pineal and thymus of a very dubious endocrine activity, the pituitary remains as the most probable of the endocrine agencies concerned. The case was far from clear cut, however, as there were missing a number of findings of pituitary disease. That the youth of the patient might be a factor in this was obvious but, lacking standards, interpretation became a matter of opinion. The little patient presented a considerable social problem. With a mentality on a parity with his age, a physique of a boy of nine, and adult sexual development, it was evident that the child would have to be safeguarded. Through the courtesy of Dr. Greene, and with the consent of the parents, the child was committed to the Fernald School with the understanding that he would be studied at six-month intervals in the hope that the trend would establish a diagnosis. The second study has just been completed (see B-1008). He has grown 8 cm. and increased 4.4 kgm. in weight. His weight is still 22 per cent below prediction, but the comment on the inaccuracy of the earlier standard still operates, the sitting height index being unchanged. His observed basal rate has increased disproportionately so that he is 64 per cent above his age prediction and but 13 below that of the area formula of Bailey. He is 6 per cent above the Harris-Benedict prediction. On this basis it seems to us possible that the interpretation of the earlier measurements was in error and that the predicted basal really lower than the higher value to which we gave the greater weight. This matter will be resolved as time goes on. The blood pressure has increased a little, the pulse is more rapid, CO_2 is diminished—this probably due to some incooperation on the part of the patient. The urine volume is now normal, but the urine shows both a very slight trace of albumin and a few hyaline casts. The protein intake is better, the residual nitrogen much lower, though still above the normal. The sugar tolerance has increased but is still below the normal. Blood sugar is now in the normal range and the leucocytic formula is substantially as before, the actual number of the white cells, however, defining a slight leucocytosis.

Radiography: The hands, wrists and knees present the same picture as before, the sella is slightly larger with the thick posterior clinoids still present. The mediastinal shadow is somewhat smaller.

Neurological findings normal, as before.

Nose and Throat Examination shows the tonsils enlarged but less evidence of infection.

Cardiogram is normal.

Eye Examination: The eye grounds are still unobtainable. The discs are now reported as yellowish.

The present picture is somewhat more suggestive of a pituitary disturbance but again falls short of any real definition. The boy's behavior has improved and he showed a much larger measure of cooperation than at the time of the first study. During his first stay in the hospital he stole some matches and set his bed on fire. During his second stay, under the same degree of supervision, there were no overt acts. He had been reported to us as a bed-wetter but in neither of his hospital stays has this been in evidence.

The boy will be examined at intervals of six months. At the present time we feel warranted in reporting him only as unclassified, though there is some suggestion here of a possible pituitary involvement. Neither this case nor the one preceding is to be regarded as showing deviation of the endocrine function of the gonads. In fact, they certainly derive from other endocrine causes than the sex glands. Presenting, as they do, however, evidences of an early maturity which has frequently been classified as due to "hypergonadism," it has seemed worth while to discuss them for the negative value which they possess.

GROUP II. HOMOSEXUAL

CASE B-408. The patient gave as her chief complaint general fatigability, general lack of endurance and interest, and mental depression. The condition apparently dated back to puberty. At the age of 17 there was a nervous breakdown, and at the age of 32 a second and more severe attack, requiring committment to a sanitarium. After eight months' stay here the patient attempted suicide with a revolver. The bullet passed through the skull, inflicting seemingly no permanent serious injury. The patient developed homosexual tendencies which first found expression at about the age of puberty. There had been at least four distinct attachments, one of which was in progress at the time of her hospital admission. The patient assumed the passive role. After her suicidal attempt she convalesced in some measure from the mental condition and ultimately returned home. Her fatigability, however, increased, and for the last few months she has been incapacitated for any sort of physical exertion.

Family History: All the members of the family were somewhat highly strung. There was no history of disease conditions of significance.

Past History: The patient reported minor ailments, scarlet fever, a severe abscess on the left thigh, tonsillectomy at the age of 21, and other events noted above. She complained of frequent headaches, not relieved by glasses. The appetite was poor, bowels were regular. She established the catamenia at 15½; the flow was regular but distinctly scanty. She had always been much underweight. She disclaimed all interest in the male sex, acknowledged her homosexual tendencies, but stated that they were under complete control. This, like several other statements, was misleading.

Physical Examination: The patient was a slightly built, thin and undernourished woman in her mid-thirties. The hips were narrow and the general body configuration that of an adolescent boy. The head showed the scars of two bullet wounds, but was otherwise not remarkable. Teeth were in fair condition. There was a somewhat asymmetrical chest expansion; the breasts were small and undeveloped. Pubic hair was distinctly masculine in distribution and the legs showed hypertrichosis. Routine neurological examination gave normal findings.

Laboratory Summary: The patient was 29 per cent underweight and somewhat below her predicted lung volume. A fairly satisfactory basal rate was 13 per cent below prediction. The blood pressure was low and the CO_2 definitely below the normal. The urine volume was scanty, protein intake was inadequate, redisual nitrogen normal. Her sugar tolerance was 50 per cent below the normal. The blood showed a very marked lymphocytosis.

Nose and Throat Examination: The examiner demonstrated infected tonsillar remnants.

Neurological Examination: The examiner defined the condition as a manic depressive psychosis of the depressed type. There was no evidence of organic nerve lesion.

Endermal Tests: The patient gave a positive reaction to egg albumin.

Radiography: The skull showed the effects of the earlier trauma but was otherwise normal.

Eye Examination: The discs were yellowish, remaining findings normal.

Discussion: The clinical and laboratory study here point clearly to an ovarian failure. It was recommended that the patient have the infected tonsillar remnants removed, eggs omitted from the diet, and that endocrine therapy be followed. In view of her suicidal tendencies it was also recommended that she be placed under restraint.

A later report shows no real improvement in the condition, but glandular therapy was exhibited for only a short time.

CASE B-530. The patient was a delinquent girl of 19 with a history of hetero- and homo-sexuality, together with other sex perversions. She had also committed petty thefts and had presented other behavior problems. She had been committed at the age of 13, six years before her admission to the hospital. As she had become obese and had developed a number of possible endocrine stigmata, she was referred to this Clinic for study.

Family History: The patient was an orphan; there are a brother and sister who are entirely normal. The family history as recorded is not informative.

Past History: As a child she had minor ailments, removal of a tumor from the left leg, tonsillectomy and adenectomy. She complained of an occasional headache, rather frequent nose-bleed for a short time a year previously, and recently had had an abscessed tooth. The menstrual history was substantially normal, with establishment at the age of 13.

Physical Examination: The patient was a very well developed, somewhat obese girl of 19. The hair on the vertex was coarse and thick. The eyes were normal; the thyroid not palpable. The hands and feet were large and symmetrical. There was a distinct flattening of the normal thoracic curve upward from the fifth vertebra. She had considerable acne on the face and chest and a minor inguinal adenopathy. The body hair was abundant but approximated the female configuration. A routine neurological examination gave normal findings. Mentally she was found to be rather slow.

Laboratory Summary: The patient was 23 per cent overweight. An unsatisfactory basal test was 5 per cent above prediction, her true rate being unquestionably lower. The blood pressure was slightly low, the temperature slightly high. Alveolar CO_2 was a low normal. The urine was normal throughout; the phthalein test slightly low; the sugar tolerance half the normal level. The blood was lymphoid in type.

Pelvic Examination showed an introitus admitting two fingers; otherwise the findings were normal.

Barany: Static labyrinth showed an almost total lack of response to stimulation. This was felt to be congenital as a growth or a toxaemia would not be likely to destroy the function of the static branch of the 8th nerve before beginning to affect the cochleal branch.

Neurological findings were substantially normal. A possible nystagmus was recorded.

Radiography: The sella was normal and the thoracic spine normal. One infected tooth was disclosed.

Cardiogram was normal.

Eye Examination: The right disc was slightly yellowish; remaining findings were normal.

Discussion: The general picture here presented suggests an ovarian failure. Ovarian medication was recommended and the patient discharged. Eighteen months later she was again admitted. In the meantime, so far as we could ascertain, she had received no medication. The laboratory picture which she presented was substantially identical with that first recorded. She had attempted to diet, but had lowered her weight by less than 2 lbs. Under wise direction and suggestion her social status had improved. Certain of the behavior problems had become less serious and she was definitely on the way to rehabilitation. She was discharged with the strong recommendation that she be given the benefit of endocrine medication. A later report records definite general improvement.

A point of interest in this and the preceding case is the persistence of a sex appetite, albeit abnormal, in the presence of ovarian failure. We have had occasion to remark this many times and in many women with wholly normal heterosexuality we have recorded a marked libido persisting for years after demonstrable ovarian failure. Extreme cases are those in which castration is the cause of the hypogonadism, and even here a loss of sex appetite is by no means the invariable rule. A male case in the next group is possibly significant in this connection.

GROUP III. CASTRATES

CASE B-42. The present case is particularly interesting as demonstrating the slight influence on the general picture which ablation of the testicles in adult years will produce. The patient had been operated upon eight years before for tuberculosis of the testicles by Dr. John H. Cunningham, through whose kindness and interest we were able to study this patient. At the time that the patient was 19 years of age he noted some irritation of the penis. There was a slight discharge and some burning on micturition. He was treated by several physicians for gonorrhea. Ultimately he consulted the referring physician, and the condition was diagnosed as a tuberculous state. One testicle was removed nine years ago, the patient being 25, and the second three months later. For some 15 years the patient has had a cough which is usually unproductive. He entered the hospital for a general survey and primarily, in a very gracious spirit of cooperation, to assist in the work of the Clinic.

Family History: The mother and two sisters died of tuberculosis; the remaining history not significant.

Past History: The patient reported measles and malaria, an earlier attack of jaundice, and the condition noted above. He had occasional attacks of vertigo, some obstruction of the right nostril, some loss of hearing in the right ear. He had a tendency to constipation and had lost about 20 lbs. since his operation. A tonsil and adenoid operation had been performed a year previously. The tuberculous condition had been apparently eradicated.

Physical Examination: The patient was well developed and somewhat underweight, the skin was somewhat dry, teeth showed much dentistry, breath sounds and vocal fremitus apparently somewhat increased on the right. Blood pressure was slightly low. The scrotum was empty. The knee jerks were reported as somewhat exaggerated and the cremasteric reflexes absent.

Laboratory Summary: The patient was 11 per cent underweight and the basal rate was 11 per cent below prediction. The somewhat low blood pressure was confirmed; the pulse rate and temperature were somewhat low. The urine presented an entirely normal picture. The phthalein output was normal. Sugar tolerance was normal. Blood constituents were normal. The blood showed a 4 per cent eosinophilia.

Radiography findings were normal throughout.

Discussion: At the time this patient was studied it was not possible for us to secure a number of the observations which have become routine in the later investigations. The significant feature of the laboratory picture is its relative normality, a borderline basal rate with somewhat low blood pressure being the only real departure from the normal. The subsequent history of this case is very striking and we believe worthy of record. At the time that the patient was seen his real difficulty lay in his profound mental depression. It was this condition rather than physical fatigability which had been progressively lowering his effort and lessening his ambition. After his operation he had returned to the small country town in which he had been born, giving up a varied and interesting career which involved

TABLE XIX

	Castrates				Mumps	
Case Number	B-42	S-197	S-261	S-1074	B-103	S-735
Sex	M	F	F	F	F	M
Age (yrs.)	34	42	59	68	20	40
Height (cm.)	169	164	167	160	155	175
Weight (kgm.)	52.9	60.7	62.8	51.8	47.0	66.9
Weight Deviation (%)	−11	+14	+18	−6	−12	−5
Lung Volume Deviation (%)	−7	−11	−20	−9	−25	+5
Basal Rate Deviation (%)	−11	−17	−15	−21	−13	−15
Blood Pressure (mm.)	106/62	120/82	128/52	124/62	104/72	106/58
Pulse Rate (per min.)	58	70	80	60	80	64
Temperature (deg. F.)	97.5	98.6	98.2	98.2	98.8	98.2
Alveolar CO_2 (mm.)	41	35	34	40	32	44
Urine Volume (cc.)	1150	1050	960	2000	720	1360
Spec. Grav.	1.022	1.014	1.026	1.015	1.012	1.018
Albumin	0	0	0	+	0	0
Casts	0	0	0	0	0	0
Sugar	0	+	0	0	0	0
Total Nitrogen (gms.)	10.64	7.13	11.07	11.85	8.46	7.28
Residual Nitrogen (%)	1.6	13.5	7.9	10.8	9.5	6.9
Phen. Sulph. Phthal. (%)	58	64	57	60	58	53
Galac. Tol.—						
Normal (gms.)	30	40	30	30	40	30
Observed (gms.)	30	20	20	20	20	30
Deviation (%)	+0	−50	−33	−33	−50	+0
Blood—						
Non-Protein Nitrogen (mgm.)	34	30	42	32	31	34
Uric Acid (mgm.)	2.8	3.0	3.8	2.6	4.0	3.7
Sugar (mgm.)	82	91	91	84	76	90
Haemoglobin (%)	90	90	95	90	85	80
Erythrocytes (10^6)	5.52	6.07	4.84	5.07	4.58	4.72
Leucocytes (10^3)	9.10	8.60	5.25	4.30	5.50	5.20
Neutrophiles (%)	68	38	47	67	60	59
Lymphocytes (%)	23	56	43	25	32	34
Eosinophiles (%)	4	1	5	1	1	5
Monocytes (%)	5	5	5	7	7	2
Misc. (%)	0	0	0	0	0	0

B-42	Male castrate (Tuberculosis of testicles).
S-197	Female, pre-menopause castrate before menopause age.
S-261	Female, pre-menopause castrate after menopause age.
S-1074	Female, post-menopause castrate after menopause age.
B-103	Oophoritis following mumps.

much foreign travel. He naturally resumed relations with the young people with whom he had grown up, and with his attractive personality and extremely interesting conversation he won the regard of one of the young women of the town. She was entirely willing to marry him, knowing in full his physical condition. Shortly after his visit to the hospital this plan was carried out. The patient found himself not only capable of erection but of intercourse with his wife which was entirely satisfactory to her. The psychological effect of this outcome was very striking. He resumed his outside interests shortly after his marriage, and moved to the West, where he organized and is conducting a most successful business in one of the larger cities. That the erectile power is not destroyed by castration after maturity is well known. This protocol is offered as a striking example both of the slight effect on the physical picture produced by castration, and the very definite influence on the patient's psychology produced by the conviction that a portion of his manhood remained in spite of his mutilating operation. The authors feel that a case such as this may explain some of the miracles which operative procedures are alleged to have wrought.

CASE S-197. This patient represents the results of castration in the pre-menopausal period studied before the menopause would normally have taken place. Her complaint on entrance was of failing vision in the right eye. She had suffered from this for the past six months. Since the initial onset of the condition there had been some improvement, but there remained an impression in her mind that the vision was circumscribed. Four years previously she had had a complete hysterectomy following which headaches from which she had previously suffered were improved. Three years previously she developed a feeling of soreness in the epigastric region, tenderness of the abdomen, and occasional vomiting spells.

Family History was entirely irrelevant.

Past History: The patient had mumps and chicken-pox in childhood, typhoid at 21, and scarlet fever 2 years ago. She has always had the headaches mentioned above. An examination of the eyes previous to her admission gave only normal results. She reported an occasional nose-bleed, recently some slight precordial pain, occasional slight palpitation. There was a tendency to constipation. The patient had been having hot flashes since her operation. The catamenia began at 14, was regular with diminished interval and somewhat profuse flow. There was continued flow for some six months prior to the operation which was necessitated by a fibroid tumor.

Physical Examination showed a well-developed and well-nourished woman; the skin was somewhat dry and wrinkled; there was slight lateral nystagmus in both eyes, not confirmed later, and slight epiphora; the majority of the teeth were missing; the tongue showed a slight tremor, the tonsils were enlarged but apparently not offending; there was a slight cardiac systolic murmur, tenderness in the iliac regions, and a few superficial varicosities on the extremities.

Laboratory Summary: The patient was 14 per cent overweight with a basal rate of —17 per cent and slightly low blood pressure. Alveolar CO_2 was low. The urine picture was normal except for the presence of a trace of sugar and a high residual nitrogen. Her sugar tolerance was half that of the uncastrated woman of her age. The blood constituents were normal. The blood was lymphoid in type.

Radiography: A gastro-intestinal series was normal. The shadow of the gall bladder was reported as slightly more dense than normal. The lungs showed some increased density.

Eye Examination showed a very slight enlargement of the blind spots and was otherwise normal.

Discussion: The patient presented a fairly typical picture of hypogonadism as we have come to recognize it by the study of female castrates. The blood pressure is a little high, but the patient is 42 years old and somewhat nervous. The basal rate and the sugar tolerance are at typical levels, while the low CO_2, as has already been noted, is a common finding in conditions depressing the activity of the ovaries. Subsequent to the examination the patient gave no evidence of gall bladder disease, suggested by the skiagram.

CASE S-261. This patient was castrated before the menopause and was examined by us after the age at which the menopause would naturally have occurred.

The patient's chief complaint was a marked fatigability. The condition dates back some 24 years in its onset, when the patient first began to exhibit a severe asthenia. Six years later a panehyterectomy was performed, the patient being 41 years of age at the time. Subsequent to the operation the asthenia increased and there were attacks of faintness and even of collapse. As the years have progressed these have become fewer in number and less severe. More recently she has developed some palpitation, tinnitus and vertigo.

Family History: The patient is one of ten children, seven of whom survive. One of the sisters has been studied in this Clinic and shown to be endocrinopathic (see Case B-37 in later "pluriglandular" paper). The family history was otherwise not remarkable.

Past History: The patient had measles three time in childhood, mumps at the age of 15, the operation already noted, and a submucous turbinate resection and a hemorrhoidectomy. She had severe headaches for a number of years, but recently they have been infrequent. She reports an abscess in the right ear 15 years ago. She was subject to head-colds. The teeth have caused a great deal of trouble. She complained of hoarseness and an irritating cough. She was subject to urinary frequency and, when unable to void, to incontinence. The catamenia was established at 13, the periods were regular and flow very profuse. Of late years she has been troubled with vulval pruritus.

Physical Examination: The patient was a well-developed, somewhat obese woman of 59; the hair was dry and scanty and the scalp showed areas of eczema. The skin was dry and there were certain pigmented areas on different parts of the body. The remaining examination showed only a slight cardiac irregularity.

Laboratory Summary: The patient was 18 per cent overweight. The basal rate was —15 per cent. The diastolic blood pressure was definitely low, the systolic slightly so, the pulse was somewhat rapid. Alveolar CO_2 was below the normal. The urine was negative. Nitrogen partition was normal. The sugar tolerance was at the prepubertal level of 20 grams. The non-protein nitrogen of the blood was above the normal. There was a definite lymphocytosis and a 5 per cent eosinophilia.

Eye Examination: Entirely normal.

Radiography: The skull was somewhat thick, the frontal sinuses obscured. There was an atheroma of the aortic arch and some pulmonary fibrosis. Remaining findings were normal.

Skin Examination defines seborrhea, eczema of the scalp and senile changes in the skin.

Barany: This test gave evidence of slight irritation, possibly toxic in origin.

Neurological Examination: No evidence of organic nerve lesion was secured. The patient was highly neurotic.

Discussion: The picture here conforms in significant findings with those to be predicted from a complete castration.

Case S-1074. This patient represents a study of a woman castrated a number of years after the menopause. Her chief complaint was of eczema which involved the hands but no other parts of the body. This condition had obtained for a number of years, being more marked in the winter time and much better in the summer. The patient stated that she washed her hands fifty times a day in plain water and three times daily with a medicated soap.

Family History: Both the parents were arthritic. The mother died of cancer and a paternal uncle was psychotic. The patient was an only child.

Past History: She had the minor ailments in childhood, scarlet fever at 26 without sequelae, and was subject to a severe dysentery every summer during young girlhood. Fifteen years ago she developed a cardiac condition which necessitated her remaining in bed for three months. Twelve years previously she had had an appendectomy, and within the year a pan-hysterectomy had been performed for a large fibroid tumor, the patient then being 67 years of age. She complained of occasional headache, a long-standing post-nasal catarrh; she had had a submucous turbinate resection 25 years before, removal of several abscessed teeth and had one tooth still discharging. During young girlhood she was constipated, and has had a tendency to this condition throughout her life. The menstrual history was entirely normal, including an uneventful menopause at 50.

Physical Examination: The patient was an elderly woman seemingly in good physical condition and good nutritional balance. The teeth showed much dentistry; the nipples were undeveloped. there was a reduplication of the first heart sound, both kidneys were low, the right kidney movable, hands showed evidence of eczematous involvement. and there was some anterior curve to the dorsal spine, but the station and gait were very good for one of the patient's age.

Laboratory Summary: The patient was 6 per cent underweight. The basal rate was —21 per cent, with relatively a somewhat low blood pressure. The CO_2 was normal. The urine volume was ample, the urine contained albumin. The residual nitrogen was high. The sugar tolerance was at the prepubertal level of 20 grams. Blood constituents and blood morphology were normal. A long series of endermal tests showed the patient not reactive to a large number of proteins.

Cardiogram was normal.

Radiography: The heart was not enlarged; the sinuses and skull were normal; the teeth showed no infection, but there were numerous bulbous roots consistent with exostoses. The lungs showed increased density and fine mottling at the apices.

Chest Examination: Normal findings were reported.

Eye Examination: There was an undefined central scotoma in the left eye which the examiner believed was due to retinal hemorrhage. Remaining findings were normal.

Discussion: The picture here presented is that of a woman of 68 in surprisingly good general physical condition. The lowered basal rate and sugar tolerance are the only real indices of endocrine disturbance. The probability would seem to be that during the years which had elapsed since the menopause (18), the patient had so far adjusted that her subsequent castration did not produce such marked changes as are normally observed in younger women.

GROUP IV. GONAD FAILURE FOLLOWING MUMPS COMPLICATED BY GONAD INVOLVEMENT

CASE B-103. OÖPHORITIS. The patient's chief complaint was of abdominal pain over the ovarian region. A few weeks earlier she had had an attack of the mumps and since her convalescence had become markedly asthenic and nervous. The pain was greater over the right ovary region, but there was a steady dull ache over the entire lower abdomen.

Family History: The mother and aunt had had pulmonary tuberculosis. One sister had some condition, the nature of which was unknown to the patient, involving the cervical lymphatics.

Past History: In addition to mumps the patient had had chickenpox, measles and pertussis. Eight years previously, at the age of 12, the appendix had been removed and there was a partial resection of a cystic right ovary. The patient matured in the following year, and her subsequent menstrual history has been entirely normal. The remaining history showed a marked constipation, a sensitivity to fish, and a vaginal discharge for the preceding two years.

Physical Examination: The patient was a well-developed but somewhat undernourished girl of 20. The parotid and submaxillary glands were somewhat hypertrophied and tender. She had a slight bilateral nasal obstruction. The breasts were of the prepubertal type. Marked hypersensitiveness was elicited over both ovaries, more pronounced on the right. Hair was abundant but normal in distribution.

Laboratory Summary: The patient was 12 per cent underweight and 13 per cent below her predicted lung volume. The blood pressure was low and the CO_2 definitely below normal. The urine was somewhat scanty, otherwise normal. The residual nitrogen fraction was high. The sugar tolerance was half the normal. Blood uric acid was somewhat high, blood sugar slightly below normal. The blood morphology was normal.

Radiography: The skull and chest were normal. There was no evidence of sub-sternal enlargement. The barium enema disclosed no disorder of the colon.

Neurological Examination disclosed no evidence of any organic neurological condition.

Bacteriological Examination: The vaginal smear showed no pathogenic organisms.

Pelvic Examination: Reported as normal except for tenderness as already noted.

Discussion: The picture presented here is typical of gonad failure. The coincidence of the patient's mumps and the development of her symptoms would make it probable that an oöphoritis complicating the mumps was responsible for the lowered functional activity. Ovarian medication was recommended. A recent report states that the patient improved definitely, later married, and has two children. Our study here was of an acute condition which has certainly been corrected—probably as the outcome of natural curative agencies.

Case B-457. The patient's chief complaint was of fatigability and asthenia, with occasional periods of extreme mental activity. He also complained of headache and insomnia. He had had orchitis at the age of 15 following a severe attack of mumps. He entered college at 19, but found it difficult to carry on his academic work because of fatigability. He stated that by concentration he was able to work very rapidly, but only for a brief space of time. He dropped out of college in the middle of his second year at the suggestion of the authorities. Since that time he had tried a variety of employments, in all of which he had failed. Shortly after leaving college he had a fall down an elevator shaft; was in bed for a month and incapacitated for work for six months. The fall produced only muscular injury. He reiterated a symptom of a feeling of pressure in the head, and to this he ascribed most of his difficulties. He also had suffered greatly from insomnia and had taken large quantities of various hypnotics to produce sleep. He had had extensive medical contacts and on several occasions had taken somewhat promiscuous endocrine therapy.

Family History: The patient was an only child. On the paternal side of the family are numerous neurotics; the father is himself extremely nervous and irritable.

Past History: The patient reported mumps as above, measles and whooping cough, the injury to the back already noted, a streptococcus infection of the neck 13 years earlier, a tendency to bronchitis, and for the last 30 years hay fever during the ragweed season. He complained of attacks of acute indigestion and of constipation. He gave a history of nocturia and a feeling of bladder irritation.

Physical Examination: The patient was a well-developed and fairly well-nourished man of 40. We quote from the examiner's record: "It was very difficult at first to elicit definite information. The patient seemed to have a very much retarded psychomotor activity and found it very difficult to remember things. He seemed very sleepy and would apparently fall off to sleep at intervals in the questioning. As the examination progressed, however, he became brighter and more alert, and at the end of about two hours became much aroused and excited over his general condition." The hair on the vertex was thin; the teeth were poor and showed much dentistry; heart action was slow but regular; the left testicle was the size of a large egg, the right slightly smaller; the knee jerks were hyperactive.

Laboratory Summary: The patient was 5 per cent underweight; his basal rate was —15 per cent; blood pressure somewhat low. The urine was normal, as was nitrogen partition. Sugar tolerance was normal. Chemical blood constituents were normal. Blood morphology study showed a slightly low haemoglobin, a slight relative lymphocytosis, and a 5 per cent eosinophilia, undoubtedly referable to his hay fever.

Radiography: The chest was normal, as was the sella; large sphenoid cells were noted.

Audiogram: The aural acuity was normal.

Neurological Examination: The patient had been defined elsewhere as a psychoneurotic. The examiner found no evidence of organic nervous disorder.

Eye Examination: The disc margins were indistinct and the discs themselves were yellowish. The blind spots were slightly enlarged.

Discussion: In general the patient presented a normal picture. His nervous instability induced a lack of cooperation which prevented the performance of a number of desirable tests. Among these was a psychiatric examination. The patient was not entirely ingenuous, being overwilling to offer massive detail in regard to his presenting difficulties with a compensatory reticence about such matters as his sex life. The laboratory picture which he presented is identical with that produced by castration of the male in adult years. In the light of present knowledge we are not prepared to ascribe his nervous instability to this condition, preferring to regard the two as existing coincidently.

TABLE XX

	Sterility	Normal Pregnancy			
Case Number	S-837	M-8		M-9	
Time	–	early	late	early	late
Parous	0	1		3	
Age (yrs).	22	29	29	34	35
Height (cm.)	162.0	157	157	177.5	177.5
Weight (kgm.)	57.8	55.2	64.1	88.7	92.6
Weight Deviation (%)	+1	+6	+23	+24	+32
Lung Volume Deviation (%)	−34	–	–	−15	−7
Basal Rate Deviation (%)	−9	+3	−6	−7	−5
Blood Pressure (mm.)	92/60	94/70	102/74	108/66	100/30
Pulse Rate (per min.)	72	90	88	70	80
Temperature (deg. F.)	98.0	98.2	98.1	97.0	97.9
Alveolar CO_2 (mm.)	44	36	33	35	34
Urine Volume (cc.)	520	910	1500	1200	3300
Spec. Grav	1.033	1.021	1.015	1.016	1.010
Albumin	0	+	0	+	0
Casts	0	0	0	0	0
Sugar	0	0	+	0	0
Total Nitrogen (gms.)	7.28	6.23	7.42	9.26	9.65
Residual Nitrogen (%)	8.0	7.4	9.1	4.6	4.7
Phen. Sulph. Phthal (%)	62	–	–	–	–
Galac. Tol.—					
Normal (gms.)	40	40	40	40	40
Observed (gms.)	< Normal	30	20	30	20
Deviation (%)		−25	−50	−25	−50
Blood—					
Non-Protein Nitrogen (mgm.)	26	–	–	28	28
Uric Acid (mgm.)	3.1	–	–	3.5	3.5
Sugar (mgm.)	86	100	100	100	91
Haemoglobin (%)	85			85	75
Erythrocytes (10^6)	4.21			4.25	3.98
Leucocytes (10^3)	5.80			8.80	8.30
Neutrophiles (%)	61	Recorded as normal		70	63
Lymphocytes (%)	38			22	32
Eosinophiles (%)	0			1	0
Monocytes (%)	1			7	5
Misc. (%)	0			0	0

GROUP V. STERILITY

CASE S-837. The patient's chief complaint as presented was a decalcification of the teeth. The condition had obtained for the last six months and the patient had been urged by her dentist to have the cause of the condition investigated. An additional factor was a sterility which the patient hoped to overcome. She had been married for something more than two years without conceiving. By inference, at least, the husband had been eliminated from the etiologic equation.

Family History was entirely irrelevant.

Past History: The patient had had minor ailments, influenza at the time of the epidemic, and a tonsil and adenoid operation at the age of 7. For the past few years she had suffered from frontal headaches. The catamenia began at 14, had always been irregular, with increase in the interval, while the flow was definitely scanty. The remaining history as given was not informative. The patient was distinctly egocentric, irritable, and incooperative, which naturally were matters of record and not of the patient's report.

Physical Examination: The patient was a well-developed and well-nourished woman of 22. There were a small sebaceous cyst on the right side of the vertex, a few palpable anterior cervical glands, a slightly enlarged thyroid. The remaining examination was not significant.

Laboratory Summary: The patient was within one per cent of her predicted weight. The basal rate was reported as —9 per cent, but the conditions of the test were not entirely satisfactory and the true value was undoubtedly somewhat lower. The blood pressure was low. Alveolar CO_2 was normal. The urine was scanty and concentrated, the protein intake somewhat low, the residual nitrogen fraction normal. Blood chemistry was normal. The blood showed a slight secondary anaemia and a relative lymphocytosis. The patient did not complete the sugar tolerance test, but the partial examination showed it to be below the normal.

Pelvic Examination: This had been performed elsewhere and was reported as normal.

Blood Calcium: The test showed 11.5 mgm., a slightly high value.

Discussion: The preparation of the case was patently incomplete. It was felt, however, that the picture was generally suggestive of a primary ovarian failure. Ovarian medication was recommended, and this was followed out. Within a comparatively short time the patient became pregnant and was later confined of a normal child. We are not informed as to the subsequent condition of the teeth, since contact with the patient was lost.

In a series of gonad failures which we have investigated a number of the subjects have given a history of sterility. During the earlier studies it was impossible to resolve this question satisfactorily, but more recently a clinic has been established for the specific study of this condition. Preliminary notices of the work have already appeared (56) and the results of the investigation will be reported elsewhere. In brief, it involves a very thorough clinical and laboratory study of both partners. The case recorded above illustrates the apparent correction of a sterility occurring more or less fortuitously, as the study of the patient was most incomplete and there were no available data for the male other than a general statement.

GROUP VI. NORMAL PREGNANCY

The status of ovarian function during pregnancy is a moot point and has already been touched upon in an earlier portion of this paper. For a number of years past one of us has been conducting somewhat extensive studies on the laboratory and clinical findings during the progress of normal pregnancy. The data from two such cases are offered here as a text for general discussion.

CASE M-8. This patient was a woman of 29 who had been married for several years and who had just become pregnant. Through the courtesy of the patient's physician and her own gracious cooperation we were able to make repeated studies at intervals of substantially two weeks, during the last twenty-six weeks of the pregnancy. Two typical protocols have been selected and the laboratory data incorporated in the table above. These may be briefly reviewed. The patient was a young woman of 29, in good general physical condition. The family history was not significant; her own past history showed no important departures from the normal, and the physical findings were substantially normal. At the time of the first examination, which was twenty-six weeks before delivery, she was 6 per cent overweight, with a basal rate reported as +3 per cent. This latter was probably slighty high, as a week later she gave the value of —5 per cent. The blood pressure was low, pulse somewhat rapid, alveolar carbon dioxide a low normal value. The urine was a low normal in volume and contained a trace of albumin. Her protein intake was below a maintenance level, as gauged by the amount eliminated. The residual nitrogen fraction was normal. Her sugar tolerance was 10 grams below prediction. Of the blood constituents only the sugar was determined, the level obtained being normal. The blood morphology was investigated elsewhere and was reported to us as normal.

The second report was secured some two weeks before delivery. The patient had increased nearly 9 kgm. in weight and was now 23 per cent above prediction. The basal rate was —6 per cent, the blood pressure higher, but still at a hypotensive level. The pulse remained somewhat rapid. The CO_2 had dropped to a level below the normal. The urine volume was ample, albumin had disappeared, but a trace of sugar was recorded. It may be said, parenthetically, that a slight glycosuria is frequently recorded during the course of pregnancy. The protein intake had apparently improved slightly, but was still at a sub-maintenance level. The residual fraction was just above the conventional normal. Her sugar tolerance had dropped to 20 grams, the level of prepubertal years, of castration and of severe functional failure. Again only the blood sugar was recorded, and that at the same normal level. The blood morphology was again reported as normal. Discussion of this case will be postponed until the data of the second case have been considered.

CASE M-9. In the study of this case we were peculiarly fortunate, as we had records of the patient's functional leval prior to conception and were enabled, through her cooperation, to carry out a continued study throughout the entire course of her pregnancy. The data secured before conception showed a moderate degree of obesity (+14 per cent), a normal basal rate with normal CO_2, a normal blood and urine picture, and a sugar tolerance at 40 grams, the normal level for a healthy woman of her age in a state of sexual rest. The first test recorded in the table was secured in the thirtieth week before delivery. The patient had increased in weight materially and was

24 per cent above prediction. The basal rate was —7 per cent, the blood pressure somewhat low, the alveolar carbon dioxide at a low normal level. The urine picture was substantially normal, except for a very slight trace of albumin, an observation of frequent occurrence in this condition. The sugar tolerance was 25 per cent below prediction. The blood composition was normal, the blood morphology indicating a slight anaemic tendency. The leucocytic formula was normal. The last test was performed during the third week before delivery. The patient had added nearly four kgm. to her weight and was now 32 per cent above prediction. The lung volume had improved, a rather usual occurrence, as has already been noted by one of us (44). The basal rate deviation was —5 per cent, the blood pressure still lower than before, the alveolar carbon dioxide slightly lower. The urine volume had increased and was in excess of three liters. The remaining findings were entirely normal. The sugar tolerance had fallen to the characteristic 20-gram level, the blood composition continued normal, the anaemia was somewhat more pronounced. There was an absolute increase in the lymphocytes, which, however, were within normal limits.

Discussion: The basal rate changes during pregnancy have already been recorded by one of us (22) in a series of cases, and the findings have been confirmed in substance by careful studies on individual patients. During the early stages of pregnancy there is a tendency for the basal rate to fall somewhat below prediction, while the terminal phase reaches a level about the same amount above. Both values (—8 to +8 per cent) fall within conventional normal limits. The curve of change, however, in any given case shows considerable variation in the individual measurements. As earlier noted (23) Sandiford has suggested that this increase depends upon the added surface caused by foetal growth. As this assumption involves uncertain extrapolations and is based upon the study of a single case, too much weight should not be given to it. The fact remains, however, that for some cause not yet clearly determined, the basal rate increases during pregnancy an average of 16 per cent above the prediction based upon the usual conventional standards. This increase will obscure any lowering of the mother's individual basal as dissociated from that of the highly active protoplasmic mass of the foetus. A lengthy discussion may not be undertaken here. It may be said, however, that if allowance be made for the superimposed effect of pregnancy with its unknown mechanism, the maternal basal rates are not inconsistent with the slight depressions incident to ovarian failure.

The lowering of the alveolar carbon dioxide without any evidence of an existing acidosis parallels exactly the frequent observation in ovarian failure. The glycosuria of pregnancy (and this is a glycosuria, as has been clearly demonstrated) corresponds with the similar phenomenon observed in numerous other conditions, among which primary ovarian failure is numbered.

The lowering of the galactose tolerance parallels exactly the changes produced by the mild and by severe functional failure and castration.

To summarzie then, the laboratory picture presented by the pregnant woman parallels closely that of non-pregnant female exhibiting a lowered endocrine activity of the ovaries. We do not feel that the case is proven, as it is recognized that pituitary changes take place during this interesting physiological event. With marked posterior lobe overactivity, however, the tolerance should sink below 20 grams, which in our somewhat extended experience has never been the case. Furthermore, the tolerance lowering appears very early in the pregnancy and at a time when profound changes of pituitary activity are neither demonstrable nor probable. Teleology would support the general thesis. We offer the observed facts and a possible interpretation which we regard as probable but certainly not established.

TABLE XXI

	Psychosis				Deaf	
	1	2	3		4	5
Case Number	B-621	B-374	S-411	S-1054	S-1690	S-813
Sex	F	F	F	F	F	F
Age (yrs.)	28	36	21	23	20	29
Height (cm.)	155.6	159.3	158.0	158.0	163.0	150.0
Weight (kgm.)	37.3	56.1	55.2	62.9	56.5	57.5
Weight Deviation (%)	−30	−6	+2	+14	+1	+9
Lung Volume Deviation (%)	+26	−6	−19	−5	+9	−20
Basal Rate Deviation (%)	−22	−19	−11	−14	−12	−14
Blood Pressure (mm.)	98/60	100/62	98/72	112/68	90/48	100/64
Pulse Rate (per min.)	76	70	76	74	70	68
Temperature (deg. F.)	98.4	97.5	98.7	98.4	98.8	98.2
Alveolar CO_2 (mm.)	36	40	31	40	39	41
Urine Volume (cc.)	1340	540	2430	1500	1090	740
Spec. Grav	1.015	1.021	1.011	1.016	1.017	1.019
Albumin	0	+	0	0	0	0
Casts	0	0	0	0	0	0
Sugar	+	0	0	0	0	0
Total Nitrogen (gms.)	6.56	6.00	14.36	8.20	11.00	6.14
Residual Nitrogen (%)	13.5	9.5	13.5	8.9	8.4	11.2
Phen. Sulph. Phthal (%)	65	64	65	56	57	45
Galac. Tol.—						
Normal (gms.)	40	40	40	40	40	40
Observed (gms.)	20	30	20	20	20	20
Deviation (%)	−50	−25	−50	−50	−50	−50
Blood—						
Non-Protein Nitrogen (mgm.)	29	33	32	26	34	31
Uric Acid (mgm.)	4.1	2.9	—	2.7	3.3	3.7
Sugar (mgm.)	70	90	100	80	100	95
Haemoglobin (%)	90	75	95	70	96	80
Erythrocytes (10^6)	4.98	4.03	5.62	3.80	5.64	4.71
Leucocytes (10^3)	11.50	5.25	9.80	6.80	7.60	11.80
Neutrophiles (%)	66	51	61	51	56	60
Lymphocytes (%)	29	42	32	39	42	29
Eosinophiles (%)	1	4	1	2	1	2
Monocytes (%)	4	3	6	8	1	7
Misc (%)	0	0	0	0	0	2

GROUP VII. PSYCHOSES

The possible association of mental disease with endocrine imbalance is probably more generally accepted in connection with changing gonadal activity than in any other potential endocrine manifestation. The puerperal psychoses, the existence of which, it is true, is denied by many, the involution psychoses of the menopause, and possibly other types of mental disturbance appearing concomitantly with evidence of disturbed ovarian function, are cases in point. As we have discussed certain psychotic conditions appearing coincidently with aberrations of both the pituitary and the thyroid, it seems appropriate to review a few of these cases in which a psychosis and a primary gonad failure occur concurrently.

CASE B-621. The patient was admitted to the clinic offering as a chief complaint epileptic seizures accompanied by vague abdominal distress. The history of the epilepsy dated back 21 years, at which time the patient was 7 years of age. She had had scarlet fever during this year, but the seizures had already manifested themselves prior to this event. Up to the time of the catamenia, which occurred at 13, they came at substantially monthly intervals. Since that time they have come at irregular periods, the quiescent interval, however, tending to be greater than in the early years. The abdominal condition had developed only a few months previously and apparently was wholly independent of the epileptic attacks. She described this condition as a definite pain at the left of the umbilicus and which radiated upward. It varied greatly in severity and in the duration of the attacks.

Family History: The patient has one brother who is normal and healthy. The family history is entirely irrelevant.

Past History: The patient reported the minor ailments of childhood, scarlet fever at 7, as noted above; a tonsillectomy and adenectomy and an appendectomy. Some years before admission she attempted to commit suicide by drinking iodine, and in addition to this there were two later psychotic episodes requiring restraint in an institution. She reported severe headaches with her epilepsy during the earlier years only. She was subject to palpitation, was constipated and complained of frequent attacks of indigestion. The menses were established at 13 and were regular but somewhat scanty. She has always been much underweight. The girl was a very simple-minded, immature individual whose presenting difficulty had caused a marked degree of isolation. Her life was very narrow and her mother, her sole associate. There has been a constant fear in later years that the mother would die and leave her alone, in which event she planned to die also.

Physical Examination: The patient was a fairly developed but much undernourished woman of 28. The lips were slightly bluish, the teeth in poor dental repair and several missing. The breasts were small and somewhat undeveloped; the heart, lungs and abdomen were normal, the knee jerks were hyperactive, and the remainding findings substantially normal.

Laboratory Summary: At the time of examination the patient was 30 per cent underweight, but definitely above her predicted lung volume. The basal rate was —22 per cent, the blood pressure definitely low, CO_2 a low normal. A trace of sugar was recorded in the urine, which was otherwise negative. The protein intake was below a maintenance level. The residual nitrogen fraction was very high. The sugar tolerance was half the normal. Blood uric acid was high and blood sugar low. There was a slight leucocytosis and a normal leucocytic formula. A report from the Boston Psychopathic Hospital,* made three years earlier, showed comparable values for the blood and urine findings and a basal rate very much higher. This latter was undoubtedly not the patient's true level. A second report from the Psychopathic Hospital of an admission a few months earlier than her admission here was again confirmatory as to the blood and urine findings. The basal rate was much lower than before, but still above prediction, and undoubtedly not representative of the patient's true basal rate.

Nose and Throat Examination gave normal findings.

Radiography: The heart, lungs, skull, sinuses and sella were all normal. The teeth showed no focal infections, but one retained root was demonstrated. A gastro-intestinal series was normal.

Neurological Examination: The examiner found no evidence of organic disease. He defined the condition as a true epilepsy.

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*We take much pleasure in acknowledging our indebtedness for this and many similar courtesies.

Pelvic Examination: The patient showed a somewhat excessive hair growth; the examination was otherwise not informatory.

Eye Examination showed slightly enlarged blind spots, but otherwise no abnormality.

Spinal Fluid was reported to us as normal.

Intelligence Quotient was reported to us as 86.

Discussion: At the time of the first admission to the Psychopathic Hospital she was discharged with a diagnosis of psychosis with epilepsy. Re-examination a few months before her entrance to this Clinic disclosed epilepsy without psychosis. The laboratory picture here presented by the patient was consistent with a primary ovarian failure, and she was discharged with the diagnosis of hypogonadism with epilepsy. The question of existing psychosis was left in abeyance. Under the direction of one of us she was treated with follicular hormone and in a few weeks her general condition had improved materially. The basal rate had become —10 per cent, the blood pressure had increased to 106, the sugar tolerance was normal at 40 grams, the blood uric acid had fallen to 3.3, and the blood sugar increased to 91 mgm. She still showed high residual nitrogen in the urine. In so short a space of time it was impossible to say what influence this improvement of her functional level could have on her major difficulty. Her general condition was certainly improved at the time of her admission for the second study.

CASE B-374. The patient's chief complaint as given by herself was indigestion, from which she had suffered for about three years, with pain apparently both in the stomach and the abdomen, though the patient's description was not clear cut. Two years previously she had been for nearly a year at the Boston Psychopathic Hospital and been discharged as unimproved, with a diagnosis of dementia praecox. The first mental deviation was noted at the age of 18 by her family, when she began making remarks which were in nowise germane to the situation or to current conversation. Subsequently she graduated from college, making the Phi Beta Kappa. Following graduation, she taught in several high schools, but a gradually increasing repugnance to this work led her to discontinue it after two or three years. She was decidedly erratic during this period. She then took a course in a business college and subsequent to this was employed in a variety of business positions, including some newspaper work. She was not successful in any of these endeavors, and ultimately she went into the missionary field. Here erotic tendencies developed and she was brought back to Boston and placed in the Psychopatic Hospital, where she remained for about a year, as noted above. From that time until her entry into this Clinic, some 2½ years later, she had remained with her family, showing steady downward progress in the trend of her psychosis.

Family History: The patient was one of a large family, the general history of which was not significant.

Past History: She reported only minor ailments, an earlier otitis media and an occasional headache. The bowels were irregular. The menstrual history was not remarkable, except for very scanty periods. The remaining history was not significant, and in some respects was independable.

Physical Examination: The patient was a well-developed and nourished woman of 36, oriented as to environment and time. The hair was normal in amount and distribution. The face showed a marked degree of brownish pigmentation, simulating the "mask of pregnancy." The breath was foul, the teeth in fair condition only. Fusiform papillæ on the anterior two-thirds of the tongue were very prominent and the glossal margin showed numerous teeth impressions. There was no thyroid enlargement. The remaining examination, including routine neurological observations, was not informative.

Laboratory Summary: The patient was 6 per cent underweight. The basal rate was 19 per cent below prediction, with very low blood pressure. The urine volume was scanty; albumin was recorded. The protein intake was apparently below a maintenance level; the residual nitrogen fraction was high. The sugar tolerance was 25 per cent below the normal. The blood was lymphoid in type; there was a 4 per cent œsinophilia and a secondary anæmia.

Eye Examination: The patient showed some symmetrical contraction of form and color fields.

Neurological Examination: The examiner defined a psychosis, probably a dementia præcox.

Radiography: Gastro-intestinal examination disclosed no abnormalities, except for probable disease in the appendix.

Pelvic Examination disclosed no abnormality.

Bacteriological Examination: A vaginal smear was normal.

Discussion: The general picture here is consistent with ovarian failure. The erotic element in the patient's complex is entirely consistent with this condition, as has been recorded elsewhere in this paper. That the psychotic condition is directly connected with the endocrine state is not a supportable thesis with such information as we have at present. Ovarian therapy was recommended, together with the necessary steps to correct existing difficulties, such as the anæmia and the pathological appendix. The subsequent history of this case is unknown to us.

CASE S-411 AND S-1054. The patient gave her chief complaint as a nervous breakdown. The more complete history was received through the courtesy of the referring physician, who stated that the patient had a brief psychotic attack prior to 1922, from which she recovered spontaneously. Again early in that year there was a period of depression which led to her commitment to the Boston Psychopathic Hospital, from which she was transferred to the Wiswall Sanitarium in February. The patient was excited, noisy and destructive and required occasional tube feeding. She remained in this condition for several months. There was a gradual diminution of the excited phase, with brief recurrence at the time of her periods. She gradually declined into an apathetic state and five months after her admission she cleared very rapidly, and in July of 1922 was sent home on a trial visit. She was readmitted on May 7, 1923, having lived an entirely normal life up to within a few days of her admission. She went through substantially the same cycle and was sent out on November, 1923. In May, 1924, she was again admitted, ran the same course of symptoms, and was sent home in September. The diagnosis established was that of a manic depressive psychosis. She was admitted here for study in late September of 1924.

Family History was not relevant. The patient is one of six children.

Past History: She reported measles, scarlet fever and chickenpox in childhood. The remaining history was entirely irrelevant, including that of the catamenia.

Physical Examination: The patient was well developed and nourished, the eyelids were inflamed, teeth were irregular and showed many fillings, there was a possible slight thyroid enlargement, the breasts were small and undeveloped, there was much hair on the chest and legs, and the pubic hair assumed the male configuration. The remaining findings were normal.

Laboratory Summary: The patient was within 2 per cent of her predicted weight. The basal rate was —11 per cent, blood pressure definitely low, CO_2 substantially below the normal. The urine volume was large, protein intake high, residual nitrogen much above the normal. The sugar tolerance was half the normal. Blood chemistry and blood morphology were substantially normal.

Neurological Examination gave no evidence of organic nervous disease.

Discussion: The patient presented a clear-cut picture of ovarian failure, with practically all of the evidences which we have learned to associate with this condition. Ovarian medication was advised.

Eighteen months later the patient was returned to us for further study. There had been one additional attack which had run the same course as the earlier seizures. She had had a series of boils in the preceding winter; the remaining history was not striking. She stated, however, that she had been under osteopathic and chiropractic treatment and had not followed the endocrine medication. The physical examination confirmed the earlier findings. There was, if anything, an increased hair growth, the external genitalia were essentially female in character and well developed. The recorded blood pressure was low. Laboratory examination showed an increase in weight of nearly 8 kgm. The basal rate was —14 per cent, the blood pressure at this time was higher than that recorded by the House Officer, but still low; the pulse was normal, as before. The urine volume was now more nearly normal; her protein intake had been cut down, but was still above maintenance. The residual nitrogen fraction was at the upper borderline of the normal. The sugar tolerance was unchanged and was half the normal. Blood composition was normal. The patient had developed a secondary anæmia and a relative lymphocytosis. Skiagrams taken at this time showed a normal sella and sinuses and a suggestion of convolution impressions on the inner table. A pelvic examination disclosed no abnormalities. The eye examination showed a very slight enlargement of the blind spots.

Discussion: The second test was highly interesting and gave confirmation of the results of the first examination in an untreated patient. Again ovarian medication was strongly recommended at the time of the patient's discharge. We are advised that it has been followed (10 grains t. i. d.), and that while the patient has had a recurrence the duration of the psychotic period has been greatly lessened. Medication is being continued.

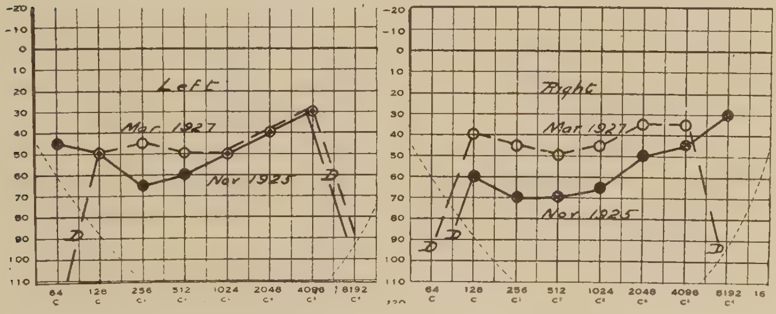
GROUP VIII. DEAFNESS

CASE S-813. The patient was a girl of 29, complaining of an increasing deafness in the left ear and a stationary loss in the right. As a child her hearing was normal. Impaired acuity was first noted at the age of 14, and then only in the right ear. At the age of 24 she found that the left ear had become involved, and this second condition had been progressive since that time. There was neither tinnitus nor paracusis.

Family History was not relevant.

Past History: The patient reported all of the minor ailments of childhood at an early age. She had influenza at the time of the epidemic, her age then being 22. In addition, she had had an appendectomy, with a later laparotomy for lysis of adhesions; two tonsillectomies and a dilatation and currettage operation for painful menstruation at about the time the second ear became involved. She complained of dull headaches, vertigo, susceptibility to colds, an abscess in the throat in 1910, and a fullness of the neck in the neighborhood of the thyroid. During the past three years she has become fatigable. She was markedly constipated and for a period of four years prior to her curettage she suffered from vomiting and pain in the right side. The menstrual history was normal and the remaining history not significant.

Plate VI



Case S-813

Physical Examination: The patient was a well-developed, well-nourished girl, whose breath was slightly foul. There were tonsillar remnants and a slight thyroid enlargement; the abdomen was normal, as was the nervous system.

Laboratory Summary: The patient was 9 per cent above her predicted weight and showed a basal rate of —14 per cent, with low blood pressure. Alveolar carbon dioxide was normal. The urine was somewhat scanty, but was otherwise normal. Her protein intake was below a maintenance level, the residual nitrogen fraction high. The phthalein output was below normal. Her sugar tolerance was half the normal. The blood uric acid was relatively slightly high. The blood showed a somewhat low hæmoglobin and a slight leucocytosis, with substantially normal leucocytic formula.

X-Ray Examination showed some obscuration of all the sinuses.

Barany Test gave normal findings.

Eye Examination gave a positive Ewing test, with slight enlargement of the blind spots.

Audiogram showed a definite loss of hearing in both ears, which were substantially alike.

Discussion: The presenting picture here was one of ovarian failure. Ovarian medication was recommended and for a time the patient followed it. The basal rate improved, also the blood pressure. There was no great change in the hearing, although some slight improvement was noted. More recently the patient has shown a return to the earlier level of hearing. She is seriously circumscribed and in anticipation of the future has begun to study lip reading. That she has not followed her medication there can be no doubt, although it is questionable if her patent endocrine defect and her hearing failure have any association. Correction of her pan-sinusitis was also recommended, but this, like her medication, has not been carried out.

Case S-1690. There are several points of interest in this case, which is one of progressive deafness in a girl of 20. The condition began at the age of 10 and was progressive for a period of about 4 years. During the past 6 years it had remained unchanged so far as the patient could tell. There had been some catarrh during the early years, but this disappeared without any improvement in the hearing. The patient had been given pituitary extract at one time, but without affecting the deafness. The patient was a frail child, but with the establishment of the catamenia at the age of 12 she became more robust and was a healthy young girl at the time of her admission.

Family History: Cardio-renal disease and diabetes appeared several times among the immediate relatives.

Past History: She reported the minor ailments of childhood, a slight attack of tonsilitis, a partial tonsilectomy at 4 and a tonsil and adenoid operation at 12, and a brief attack of pyelitis at the age of 10. The patient reported a discharging ear early in the period of her deafness. This was, however, of brief duration. The remaining history, including that of the catamenia, was essentially irrelevant.

Physical Examination showed a well-developed and well-nourished girl. The speaking voice had the peculiar quality so frequently noticed in the deaf. There was excessive pilosity of arms, legs and spine, but the configuration of the pubic hair was normal. There was some acne on face and chin. The patient was distinctly deaf, but could apprehend loud speech. The blood pressure was low. The remaining findings were normal.

Laboratory Summary: The patient was within 1 per cent of her predicted weight. The basal rate was —12 per cent, blood pressure low, carbon dioxide a low normal. The urine and blood findings were normal, except for a slight lymphocytosis. The patient was in college and it was suggested that the tests of sugar tolerance be performed there. The whole general picture of the patient suggested an ovarian failure. Twenty grams of sugar were sent and the test was reported as negative. Later, a 40-gram test was also reported as negative. Sixty grams were sent, but as it was approaching vacation time the patient waited until she returned home to complete the test. In the meantime, examination of the existing data confirmed the earlier opinion of a probable gonad failure, with which the sugar test was wholly at odds. On the return of the patient to this neighborhood the sugar test was repeated with an initial dose of 20 grams, to which the patient gave a positive response. A second 40-gram dose gave a very marked positive response, while the response to 10 grams was negative.

Nose and Throat Examination: Tonsillar remnants were noted, but were apparently unoffending. There was a deflected septum, producing partial obstruction.

Ear Examination gave normal findings.

Barany test indicated normal conditions.

Audiogram: Marked uniform loss of hearing in both ears was disclosed.

Radiography: The sinuses were all normal. The patient showed one unerupted molar.

Discussion: The repeated sugar test completed the picture of a definite primary ovarian failure, and treatment with follicular horhome was recommended. It may well be argued that as the patient's deafness began before the establishment of the catamenia that there could be no connection between her presenting difficulty and her patent endocrine defect. We are wholly unwilling to attempt to establish any artefactural relationship between the two conditions. Recommendation for treatment of the endocrine condition was made solely to normalize the patient's general metabolism. That any betterment to the ear condition could accrue was wholly problematical. It should be said in passing that many of the subjects of deafness studied by us who demonstrate endocrine defects show a deafness which derives from a definite and demonstrably non-endocrine cause. The normalization of the endocrine status of such patients can only influence the hearing defect by indirection, if at all.

TABLE XXII

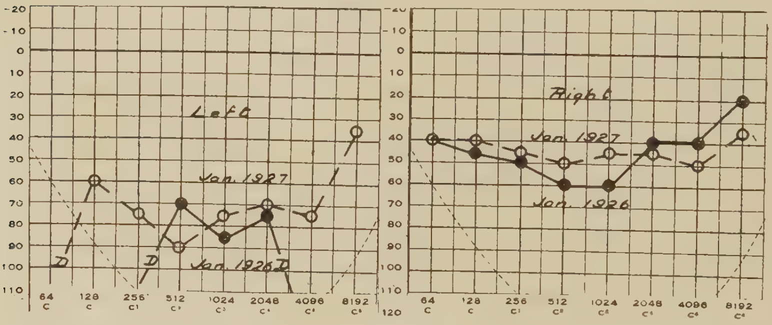
			Obesity			
	Genital Arrest		Castrate	Functional	Functional Failure	Azoospermia
Case Number	B-441	S-952	B-50	S-1229	B-610	S-1402
Sex	F	M	F	F	F	M
Age (yrs.)	21	10	51	39	15	27
Height (cm.)	148	146	154	159.0	142.7	180.5
Weight (kgm.)	46.6	5.5	110.0	94.5	39.5	84.5
Weight Deviation (%)	−2	+34	+107	+65	+7	+8
Lung Volume Deviation (%)	−33	−9	−58	−37	−15	+2
Basal Rate Deviation (%)	−17	−1	−17	−17	(+2*)	−3
Blood Pressure (mm.)	86/58	100/65	180/94	150/88	90/44	120/70
Pulse Rate (per min.)	76	86	56	67	72	72
Temperature (deg. F.)	97.2	99.6	97.0	97.8	98.2	97.2
Alveolar CO_2 (mm.)	42	38	36	40	36	44
Urine Volume (cc.)	1180	1040	720	720	500	880
Spec. Grav	1.019	1.032	1.027	1.029	1.015	1.032
Albumin	+	0	0	0	+	0
Casts	+	0	0	0	0	0
Sugar	0	0	0	0	0	0
Total Nitrogen (gms.)	10.44	14.60	8.46	6.55	4.43	14.00
Residual Nitrogen (%)	15.1	6.6	11.3	6.6	4.9	11.0
Phen. Sulph. Phthal (%)	62	67	42	52	53	49
Galac. Tol.—						
Normal (gms.)	40	30	20	40	40	
Observed (gms.)	20	30	20	30	20	not done
Deviation (%)	−50	±0	±0	−33	−50	
Blood—						
Non-Protein Nitrogen (mgm.)	27	33	33	27	37	29
Uric Acid (mgm.)	3.0	2.9	5.3	3.0	3.7	3.7
Sugar (mgm.)	91	(118)	(113)	107	93	90
Haemoglobin (%)	100	85	100	70	80	90
Erythrocytes (10^6)	5.30	5.56	5.12	3.80	4.80	4.50
Leucocytes (10^3)	10.20	13.20	7.70	9.80	6.50	9.40
Neutrophiles (%)	69	75	32	69	44	71
Lymphocytes (%)	24	20	54	27	44	20
Eosinophiles (%)	1	0	10	1	3	3
Monocytes (%)	6	5	2	3	9	6
Misc. (%)	0	0	2	0	0	0

GROUP IX. DEVELOPMENT ARREST

CASE B-441. The patient was a 21-year-old girl whose chief complaint was of physical and mental retardation. She was also very deaf in the left ear, less so in the right. The patient was an eight-months baby, and at birth was not expected to live. She showed developmental retardation from birth, being 4 years old before she began to talk. The developmental retardation has been even more marked since her fourteenth year, at which time the periods first appeared. Her deafness also dated back to early childhood. There was no paracusis, some tinnitus and no apparent change in her deafness for some years past. The various deficiencies had brought about a shut-in existence, though the patient was not outspokenly asocial.

Family History: Twin sisters of the patient died a few hours after birth. There were several other surviving children, all of whom were normal.

PLATE VII



Case B-441

Past History: The patient reported minor ailments and a tonsil and adenoid operation at 17. The remaining history, including that of the catamenia, is entirely uneventful.

Physical Examination: The patient was of small stature and fairly well proportioned, although the chest and hips were relatively somewhat large. There was a marked hair growth on the arms and legs and the heavy pubic hair showed a masculine type of distribution. There was obviously marked mental retardation. Much acne was observed on both face and back. Both ears were deaf, the right less markedly so. Some tonsillar remnants were noted. There was a loud systolic murmur at the cardiac apex transmitted to the axilla, a systolic murmur over the base transmitted to the neck and more pronounced over the aortic area.

Laboratory Summary: The patient was less than 5 feet tall; her sitting height index was high, so that she was actually overweight instead of the 2 per cent below prediction which was recorded. The basal rate was —17 per cent, with low blood pressure. Both albumin and casts were reported in the urine and the residual nitrogen was very high. The sugar tolerance was half the normal level.

Radiography: The skull was normal.

Audiogram: The patient showed a marked loss of hearing in the right ear, and positive hearing in the left was obtainable only at frequencies of 512, 1024, and 2048 (see plate).

Neurological Examination disclosed gross change in the 8th nerve and various vegetative disturbances.

Ear Examination: The drums were retracted and the cones of light were broken.

Pelvic findings were normal, except for the excessive hirsuties.

Eye findings were apparently normal.

Discussion: The patient presented a picture strongly suggesting ovarian failure. Attention is called in this connection to the high sitting height index, a condition on which comment has already been made. She was placed on ovarian medication (follicular hormone), and one year later was returned to the Clinic for brief study. The height was unchanged, but she had increased 4 kgm. in weight. The basal rate was —9 per cent and the blood pressure 110/60. The lowered sugar tolerance had become normal, 40 grams being necessary to produce a positive response. The audiogram showed a striking improvement (see plate). There was also said to be definite evidence of clinical betterment.

Case S-952. The patient was a boy of 10 who was referred for obesity, genital arrest, and feminine contour of body. Prior to the time of birth the mother became very toxic and delivery was advised in the seventh month. She carried him to term, however, and was delivered by a high forceps operation. He weighed 9½ pounds at birth, but the genitalia were very small. He did not talk until he was 3 years old. At 4 he had a severe case of whooping cough, followed by bronchial pneumonia. Since then he had had frequent recurrent attacks of bronchitis. The obesity developed after the pneumonia. He had always shown a preference for female companions and was constantly seeking to be kissed by his female relatives, but within the last few months he had begun to play only with boys and had lost his desire to be fondled. He had made an unusually good record in school and had shown unusual musical gifts.

Family History was irrelevant.

Past History: Only minor ailments of childhood in addition to the record given above were reported. A tonsil and adenoid operation was performed 3 years ago. He had an occasional severe headache. Some years previously "a gland in the middle of the neck became inflamed, but subsided spontaneously." He was constipated when very young.

Physical Examination: The boy was an obese lad of 10, with very wide hips, very small genitalia, and large breasts of the feminine type. There was a large pad of fat below the umbilicus. The very small testicles while being examined were retracted into the ring. The boy showed third degree flat-foot and no pilosity.

Laboratory Summary: The boy was reported as 34 per cent overweight, with a fairly normal sitting height index. The basal rate was 1 per cent below prediction, blood pressure low, and the pulse somewhat rapid. There was a slightly febrile temperature, and if correction were made for this it would reduce the basal rate deviation to about the low normal level. The sugar tolerance was normal; in fact, all of the other observations were normal, with the exception of a slight leucocytosis.

Radiography: The skull was normal.

Eye Examination: Normal.

Discussion: The picture presented here was similar in kind to that produced by castration. The boy was reported by us as a congenital gonad failure. As there was no reason to anticipate betterment from any of the suggesting methods of treatment, no recommendations as to therapy were made. The boy was requested to return in 2 years for a repetition of the study.

GROUP X. OBESITY

CASE B-50. The patient was an extremely obese woman 51 years of age who had had a pan-hysterectomy 28 years before. She was married 30 years earlier, and in the brief interval of 2 years conceived twice, but each time induced abortion in the second month. A hysterectomy was then performed, although the patient did not know the reason for this operation. She weighed 135 pounds at the time of her marriage. After her operation she began to increase in weight and a year before she was admitted to this Clinic weighed over 260 pounds. She stated that diet was ineffective in weight reduction, but that for 15 years past she had been taking thyroid intermittently, at times reaching 8 grains a day. She stated that under thyroid medication she always lost weight, but became very weak and suffered from palpitation. She had been without medication for some time prior to her admission. She also complained of a throat trouble which began 15 years before and consisted chiefly of a dry, scratchy sensation.

Family History: One sister had diabetes. The remaining history was irrelevant.

Past History: In addition to the matters detailed above, the patient reported minor ailments, diphtheria, typhoid, influenza, and frequent attacks of pharyngitis. She had had some loss of hearing in the left ear for many years. The teeth were in fair condition. She complained of attacks of hoarseness. The gastro-intestinal history was entirely normal. She denied venereal disease, and we were unable to secure the information on this point that we desired. The Wasserman reaction was negative. She complained of some nocturia. The menses were established at the age of 12 and the history was uneventful up to the time of her operation. She had used alcohol freely throughout her life.

Physical Examination: The patient was a very obese woman of 51, the trunk being relatively more obese than the legs. The pupils were sluggish in their reaction to light, but reacted well to accommotion and were equal and regular. The tongue showed no tremor, the teeth were in poor condition, there was no thyroid enlargement, the breasts were very large and pendulous. Coarse, bubbling rales were noted, most marked at the end of expiration and confined to the right side. They were increased by coughing. The blood pressure was very low. The abdomen was normal. The routine neurological findings were normal.

Laboratory Summary: The patient was just over 5 feet tall and 107 per cent above her predicted weight. Her sitting height index was substantially normal. There was marked loss in lung volume. The basal rate was —17 per cent, with a somewhat slow pulse and a hypertensive blood pressure. Alveolar carbon dioxide was low. The urine was somewhat scanty, otherwise not remarkable. Residual nitrogen was high; the phthalein output below the normal. The patient gave a positive test with 20 grams of galactose, the level to be predicted from the history of her earlier operation, and negative with 10. There was a high blood uric acid, a marked lymphocytosis, and a 10 per cent œsinophilia.

Ear Examination: The drum heads showed a moderate degree of chronic catarrhal thickening. In addition, the examiner found evidence of a low degree of toxæmia affecting the auditory nerve.

Nose and Throat Examination: There was a slight septum deviation, somewhat large, cryptic tonsils, and a slight inflammatory condition of the larynx.

Radiography: The skull and chest were normal, though the plates of the latter were somewhat unsatisfactory because of the thick chest wall.

Discussion: The whole history of this case, coupled with the laboratory examination, suggests an obesity arising from the patient's surgical hypogonadism. There is no suggestion here of thyroid failure which could not equally be referable to the ovarian loss. The œsinophilia and high blood uric acid would carry a suggestion of pituitary involvement, which was, however, denied by certain of the other observations. We were not able to complete the study on this patient and the chest condition, and that of the cardio-vascular system remained largely unevaluated. The patient was recommended to take ovarian medication, but the habit of years determined her to continue with the thyroid. We speedily lost track of her, but one of us learned later that she had become psychotic and had died within a few years of the study at the Boston Psychopathic Hospital. As noted above, complete cooperation could not be secured and the study, of necessity, remained incomplete.

CASE S-1229. This patient was a very obese woman, 39 years of age, who complained of cramp in the upper abdomen. The onset of this condition had been a few days before. She also complained of her obesity, which apparently began in young girlhood. For a number of years she had been increasingly fatigable, and with the onset of the pain element had become nervous and irritable. There was reason to believe that this latter factor was of materially longer duration than the preceding few days.

Family History: There were numerous records of cardio-renal and cardio-vascular disease in her immediate family.

Past History: She reported the minor ailments of childhood, a tendency to infections of the respiratory tract, and rheumatism. She had had tonsilitis and endocarditis in 1917. She had worn glasses for the last 5 years, and when tired was unable to focus the eyes properly. She had had several attacks of conjunctivitis in the left eye within the past few months. She was troubled with flatulency, but only when nervous and tired. The catamenia was established at the age of 11; the periods were regular at 42-day intervals, the flow was scanty.

Physical Examination: The patient was a very obese woman with the fat generally distributed, presenting hypertrichosis on the face, heavy hair growth on the arms and legs, and masculine distribution of heavy pubic hair. The palms of the hands showed a slight eczematous involvement. The majority of the teeth were missing, and those remaining were in only fair condition. The tonsils were hypertrophied and apparently not offending. There was a slight systolic murmur and a slightly high blood pressure. The remaining findings were not remarkable.

Laboratory Summary: The patient was 65 per cent above her predicted weight, with normal sitting height index. She was definitely below her predicted lung volume. The basal rate was —17 per cent, the blood pressure somewhat high. The urine was scanty and concentrated, but otherwise normal. The sugar tolerance was somewhat depressed; blood composition normal, but with some degree of secondary anæmia.

Eye Examination: The left upper form field was somewhat cut, due to a drooping eyelid; the remaining findings were normal.

Discussion: Only a limited study could be made on this patient and emphasis was laid on the purely endocrine aspects. The picture presented was suggestive of primary ovarian failure, although a pituitary dysfunction was not excluded. Ovarian medication was recommended and we believe has been followed in some measure. Indirect report suggests some but not striking improvement.

GROUP XI. FUNCTIONAL FAILURE IN EARLY ADOLESCENCE

CASE B-610. This patient was a 15-year-old girl whose presenting difficulty was her small stature, she being but 4 ft. 9 in. tall. From the time of her early childhood she had been smaller than the other girls of her own age.

Family History was entirely irrelevant. Three siblings died in infancy of diphtheria, and five surviving brothers and sisters were all normal.

Past History: The patient had influenza at the age of 7 and pneumonia a year later. The catamenia was established eight months before, and in this interval the patient had had four periods which were substantially normal. The remaining history was not significant.

Physical Examination: The patient was a small, well-developed and well-nourished girl of 15. There was a very slight thyroid enlargement, a few moist rales at the right apex, increased vocal fremitus in the interscapular region; the knee jerks were sluggish. The remaining findings were completely normal.

Laboratory Summary: The patient was 7 per cent above her predicted weight, with normal sitting height index. The basal rate as recorded was 2 per cent above prediction. This was incorrect and the test was not entirely satisfactory; the true rate was undoubtedly below this level. A second examination could not be secured. The blood pressure was definitely low, as was the carbon dioxide. The urine was scanty and contained albumin. The protein intake, as indicated by the nitrogen elimination, was below a maintenance level. The residual nitrogen fraction was normal. The sugar tolerance was half the normal level. The nitrogenous elements of the blood were slightly high. The blood showed a relative lymphocytosis and a 3 per cent eosinophilia.

Radiography: The bone development of the knees and shoulders was normal; the sella shows enlarged posterior clinoids.

Discussion: This case again could be regarded as one of pituitary dysfunction. The bulk of the evidence, however, was more suggestive of an inadequacy of gonad function. She is reported as improved, but we have had no further contact with her.

CASE S-1402. The following case is particularly interesting in view of certain beliefs that have been generally current during the past few years in relation to bodily vigor, libido and the status of the male gonads.

The patient was a large, powerful man of 27, whose complaint was of sterility. He had been married for about two years and had had satisfactory intercourse every night since his marriage, with the exception of two or three intervals of 3-4 days each. He had no difficulty in securing an erection, but believed that his ejaculation time was somewhat rapid, as he would have his orgasm within twelve or fifteen strokes after immission. His deduction is not necessarily correct, as both he and his wife always have orgasm. In 1917, ten years previously, he had had the mumps with orchitis as a complication. Several examinations since marriage had shown a complete absence of spermatozoa from the semen.

Family History showed one case of cancer, but was otherwise irrelevant.

Past History: In addition to the mumps he reported the minor ailments of childhood, scarlet fever, influenza at the time of the epidemic, and recurrent sore-throats in childhood, with one quinsy. He had headaches as a boy; none for several years, however. The remaining history was entirely normal. The patient was the driver of a truck, handling groceries in bulk, such as barrels of sugar and large cases of canned goods. He worked from 3 a. m. to noon, and acknowledged that "at times he felt tired at the end of the day's work." Three years previously he had strained his side in lifting a barrel of sugar, but examination showed it to be no more than this, and he had had but little subsequent trouble from it.

Physical Examination showed a very well developed, muscular young man. The nose showed some obstruction and the presence of a serous discharge (the patient had a head cold); the teeth were in fair condition only; the tonsils were somewhat hypertrophied. A few moist rales were noted at the right apex. Body hair was normal in amount and distribution. The testicles were less than half the normal size and there was a small left varicocele. The remaining findings were normal.

Laboratory Summary: The patient was nearly six feet tall; he was 8 per cent overweight and slightly above his predicted lung volume. The basal rate was entirely normal, as were the complementary measurements. Only the temperature was slightly low. The urine had a slightly low volume, but elimination was fair. The residual nitrogen fraction was high; the remaining findings normal. The blood cells showed a predominance of neutrophiles and a 3 per cent eosinophilia. The blood uric acid was relatively high, the serological findings were normal.

Laryngological Examination: The tonsils were found to be definitely infected.

Cystoscopy showed a small degree of posterior urethritis.

Eye Examination: The blind spots were slightly enlarged.

Genito-urinary Examination: The two lobes of the prostate were slightly enlarged and boggy. Several condom specimens showed complete azoospermia.

Neurological findings were normal.

Discussion: We regard this case as peculiarly informative. The patient is a young man with markedly atrophied testes and seemingly a complete loss of spermatogenic function. Physically he is vigorous, hardy and strong beyond the average. Sexually, his libido and his power to have intercourse, satisfactory to himself and his partner, is distinctly above the average. Diagnoses of hypergenitalism have been made on a less enduring performance than is his, and yet there is a demonstrable gonad failure so far as the exocrine function is concerned. We do not attempt to explain it. We only offer the facts.

Review of the preceding protocols demonstrates one striking difference between the cases presented and those recorded in the earlier thyroid and pituitary papers. A number of them derived from a mutilating operation with complete removal of the endocrine organs. For these, naturally, no effective treatment was available. Some of the others resulting from functional failure were placed under endocrine medication and responded favorably. In many instances, however, recourse to endocrine therapy was seemingly ineffective. This outcome must be regarded as the result of several factors. In the first place, review of the individual case protocols will disclose a record of many incomplete studies, left so because of the incooperation of the patient. Comment has been made in the body of the paper on the personality change frequently associated with ovarian failure. This has operated not only to lessen the thoroughness of the particular individual studies but also has hindered a faithful performance of the therapeutic program suggested. A second factor is found in the inadequacy of the medication. Many ovarian preparations apparently are relatively inert and the huge dosage which would be necessary to secure adequate response is but seldom offered. As already noted in the pituitary paper, one prime factor in the frequent statement that anterior lobe medication is ineffective rests upon the failure of the physician in charge of the case to prescribe an adequate dosage. As recorded in the earlier paper, one of the patients in the pituitary series showed definite improvement only with a level of medication of 104 grains of anterior lobe material daily. Many others seemingly required a daily intake of from 50 to 75 grains to restore them to a normal functional level. Thanks to the brilliant work of several investigators, among whom Doisy and Allen (57) should not fail of mention, more active ovarian material is now available for clinical use. Results obtained with this are far more encouraging and productive in our experience than was usually the case with the earlier preparations. The subject is a large one and equally one of great importance. It is planned by one of us (C. H. L.) to present in the near future a much more extended analysis of the results of ovarian therapy than could suitably find place in this article. It is permissible, however, to say that in the more recent cases in which ovarian therapy has been indicated by the establishment of a diagnosis of primary ovarian failure, the results are far more encouraging and hopeful than was formerly the case. While these materials have not been available for a sufficiently long time to allow for such thorough studies of the results of medication as are available for the pituitary and the thyroid investigations, the trends of betterment disclosed warrant the same degree of confidence in the validity of diagnoses as are given by the results of therapeutic testing in pituitary and thyroid disorders.

The cases in the foregoing section were selected to illustrate some given point as strikingly as possible. Many of the other cases in the series presented uncomplicated functional failures, and a large part of these have responded satisfactorily to treatment. As cases, they are lacking, however, in the distinctive special features of those selected for this series of protocols and their consideration belongs more properly to the forthcoming paper which will be devoted primarily to a discussion of the results of treatment.

The authors wish to express their sincere and grateful thanks to the colleagues and associates who as members of the staff have contributed so much to their studies, to their other colleagues from whose reference have derived many of the interesting and significant cases in the series and finally to the patients themselves for their cooperation in the work.

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The original publication of the paper on the Adrenals followed the one on the Pluriglandular Syndromes. In this compilation it is placed in its natural order.

This paper was published in the first number of Volume 13 with which a change in page size was made, necessitating a resetting to conform to the former papers. This resetting has destroyed the original pagination and the paper is treated as a unit and paged beginning with 1. Complete reference to the original publication will be found at the close of the paper.

STUDIES OF THE ENDOCRINE GLANDS

V. The Adrenals

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In a series of previous papers the authors have described an objective method for the diagnosis of endocrine disorders (1) and the results obtained from its application to several of the recognized members of the endocrine group (2). The present paper presents the results which have been obtained with the few adrenal cases which we have been privileged to see. Contrary to the relative frequency with which pituitary, thyroid, and ovarian disorders are encountered, demonstrable adrenal disease seems to be of very rare occurrence. Osler (3) saw only seventeen cases of Addison's disease in the course of twenty-one years. Boothby and Sandiford record but thirteen Addisonians in a series of two thousand four hundred and seventeen (2417) cases studied at the Mayo Clinic. As they report over six thousand thyroid cases in a parallel series, the relative infrequency is strikingly illustrated, particularly as these two groups are drawn from material many times as extensive. In other words, cases presenting the classic signs of adrenal disease as described by Addison, are most infrequently encountered. That the syndrome is implicit in disturbed function of the adrenal glands is generally accepted, although Lewin's (5) collected series of five hundred and sixty-one cases included 12 per cent without demonstrable lesion, a finding frequently recorded by other and later observers. Further, opinion is by no means unified today as to the relative importance of the cortical and medullary portions in determining the disease picture. In spite of these and other seemingly contradictory observations, the intrinsic association of lowered adrenal activity with the Addisonian syndrome may be regarded as definitely established. A similar authority does not obtain for that other type of adrenal failure which is assumed to result from a lowered functional activity and to be unassociated with gross anatomical changes in the gland. This syndrome, possessing many of the characteristics of Addison's disease, such as asthenia, hypotension, and usually emaciation, has been in large measure developed by the work of the French clinicians, [See among others, Sergent (6) and Lucian and Parisot (7)], while in this country, Sajous (8) has been the earliest and major contributor in defining this condition. Incidentally, it should be said that this syndrome more nearly equates with the picture of adrenal insufficiency as produced in numberless animal experiments involving interference but not complete extirpation. A complete Addisonian has yet to be produced experimentally. A third type of failure, chiefly associated with suprarenal hemorrhage, is an acute condition usually terminating fatally in a few days. In addition, a variety of intermediate states have been described but they lack clarity of outline, and in many instances depend upon a mass of wholly unproven assumptions for their very existence. Of the many so-called pluriglandular syndromes, in largest measure also the work of the French school, although clinicians of all nations have synthesized diverting combinations of impressive intricacy, but little notice need be taken. The endocrine glands severally and individually are among the potent regulators of general metabolism. In the impairment of one, as in a similar condition with any of the equally important non-endocrine factors, havoc is wrought in many of the delicately balanced equilibria associated with normal function. In the disturbances thus engendered, it is inevitable that other endocrine as well as non-endocrine foci will participate, and in their several dysfunctions influence the terminal disease picture. But their participation is secondary and resultant, not primary and causative. To illustrate, the amenorrhoeas of thyroid and pituitary failure need not derive from the primary failure of the endocrine activity of the ovary any more than when the condition arises in non-endocrine disease wholly unassociated with the generative system. The use of ovarian extract to combat this condition is as illogical as it is ineffective.

In the following paper in this series we analyze the 22 pluriglandular cases which have come under observation in the course of examination of nearly four thousand patients. It is enough to say here that with but minor exception the pluriglandular element derives from the superposition of surgical ablation of one gland upon the functional disturbance in another. In a single case, unique in our experience, we observed both a surgical dysthyroid state and partial castration added to a probable pituitary dysfunction, which was seemingly the original endocrinopathy.

Reverting to the immediate thesis, we find a well established entity in Addison's disease and one equally demonstrable in the acute and rapidly fatal condition, deriving from hemorrhage in the gland. Of the third for which, of the many presenting, we will select the term ''hypo-adrenalism,'' there is a less certain foundation of proven and tested fact, yet enough authoritative observations exist to render consideration necessary.

Frank under-function would seem to connote the existence of an antithetical picture in which a complementary over-activity of the gland is manifest. In the earlier paper on the gonads (2) we have recorded our failure to observe such a condition in our cases involving the primary sex organs. With the adrenal, however, several well marked and rather striking anomalies are frequently associated with alleged hyperactivity of the gland, and brief analysis of these is germane to the text.

Precocious puberty is frequently associated with tumors of the adrenal cortex, and the assumption made that hypernephromata condition an overactivity of the gland. Unfortunately for clarity of definition, the same series of somatic and functional changes have been associated severally with the thymus, pineal, the gonads themselves, and less dubiously, the anterior lobe of the pituitary.* The lack of etiological specificity here greatly enhances the difficulty of the diagnostic problem. Tumor development in adult years is believed to result in an inversion of sex characteristics to which the term ''virilism'' is usually applied. Cases are also recorded in the pre-adolescent period. The condition is largely confined to the female sex and is intrinsically a masculinization of the secondary sex characteristics. It should not be confused with precocious puberty which is, as the name implies, an abnormally early maturation along wholly normal lines. Virilism connotes an inhibition of the exocrine manifestations of the sex involved. Modification in the differential sex distribution of body hair (hirsutism) is but one item in the general picture of virilism. It may occur alone, however, or at least without well marked evidence of the other features of a true virilism. It has frequently been recorded in connection with ovarian changes, and it is interesting to note that in the eight cases cited by Falta (9) to associate hirsutism with tumor of the suprarenal, five patients had coincident pathologic changes of the ovary, one ''small'' ovaries, and in the case of the other two no statement is made concerning the gonads.

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*The literature is fairly extensive, and excellent summaries are to be found in several texts, which emphasize the clinical aspects of endocrine disorders.

Another genital anomaly presenting diverse manifestations is pseudohermaphroditism. True hermaphroditism has practically never been certainly observed in man. Neugebauer (11) cites only five established cases of a single ovotestis. Neumann (12) has recorded some later cases in which there may be a larger measure of support for the thesis, but he is skeptical of the accuracy of the conclusions drawn by the authors in many of the cases which he cites. Burden (10) records a case with independent ovaries and testes on each side. Falta seemingly regards the condition as possibly arising from aberrant adrenal function, a position which has apparently been rather generally adopted [Glynn (13)]. To support his thesis, Falta cites the fact that Neugebauer, in his comprehensive work on the subject, records thirteen cases showing disorder of the adrenals. Inasmuch as Neugebauer records over twelve hundred observations, and further, as in this series he reports sixteen cases each showing neoplasm of ovary or testis, the warrant for so sweeping a generalization would seem to be lacking. Further, several of Falta's quoted supporting cases showed simultaneous involvement of the gonads. The rare conditions designated as ''progeria'' [Gilford (14)] and ''nanism type senile'' [Variot and Pironneau (15)] would seem to have but tenuous claim to a purely suprarenal etiology. To summarize then, while the adrenals apparently exercise some influence over the genital sphere, it is far from well defined and is very far from being a unique attribute of this member of the endocrine group. Further, the assumption a priori that cortical tumors determine an over-activity, but ill equates with the observations of neoplasms of the thyroid or pituitary. Lastly, those pictures which may with most certainty be correlated with adrenal disease fail signally to present a uniform antithesis to that offered by the established failure producing Addison's disease.

As the adrenal is essentially two glands, there should be several dysfunctional possibilities, and conceivably certain of the conditions already touched upon could fall in this category. Unfortunately our knowledge of adrenal disease in man is very limited, and the essential nature of its function precludes those surgical interventions that have done so much to clarify our knowledge of certain of the other endocrines. There is, of course, a vast number of most interesting and informative data in relation to animal experiments. As the vast majority of these were designed to throw light on certain physiological problems, data that are applicable to clinical conditions are in the nature of by-products. Further, as we have emphasized in earlier writings, the metabolic divergences of the several species make difficult if not impossible an equation with man. Finally, the results of acute experiments cannot be translated into terms of the chronicity of human disease. Happily, Addison's disease is a rock in the troubled sea of conjecture, surmise, and assumption, and its study offers a sure line of approach to the better comprehension of one phase of disturbed adrenal functions. The carefully recorded clinical and laboratory studies of this condition are of the greatest value.

Turning to our own brief series, we must acknowledge initially some difficulty in classifying all of the composing members. Accepted opinion warrants the designation of the Addisonians as hypofunctional cases (I). Far less clear cut are the indices of functional level in the few other case (II) that we record. In

TABLE I

CLASSFICATION OF CASES

I	Addison's Disease	3
II	Hypo-adrenalism, probable	6
	Hypo-adrenalism, possible	3
III	Pubertas Praecox	1
	Total	13

one or two even, doubt exists as to the warrant of inclusion with the seemingly established adrenal cases. As they conform, however, to the criteria established, and as further, they have shown interesting response to the exhibition of adrenal medication (to be discussed later), we feel that they may be included with a frank statement of their dubious character. A single case of "pubertas praecox," seemingly deriving from an adrenal condition, constitutes a third group (III). For the sake of clarity, the composition of the series may be tabulated and in the subsequent summaries the data from each group will be collated separately.

We have had contact with two other cases of Addison's disease (one of them without pigmentation but with diagnosis verified at autopsy). As they were not completely studied, they are omitted from the series. Such measurements as were obtained, however, are in strict accord with those of the cases reported.

TABLE II

Physical Measurements

Observation		I	II	III
Sex	Male	1	3	0
	Female	2	6	1
Age	High (yrs.)	61	62	
	Low (yrs.)	32	22	
	Average (yrs.)	**47**	**38**	**7¾**
Height	High (cm.)	177	175	
	Low (cm.)	158	154.5	
	Average (cm.)	**166**	**165**	**115**
Sitting Height	High (cm.)	92	96	
	Low (cm.)	85	84	
	Average (cm.)	**87**	**88**	**64**
Sitting Height	Index Average	**0.524**	**0.533**	**0.557**
Chest	High (cm.)	80	107	
	Low (cm.)	69.5	61	
	Average (cm.)	**73.5**	**75**	**56**
Weight	High (kgm.)	61.4	89.0	
	Low (kgm.)	48.0	34.8	
	Average (kgm.)	**53.2**	**56.0**	**22.0**
Area	Average (sq. m.)	**1.57**	**1.60**	**0.82**
Lung Volume	High (cc.)	2200	4100	
	Low (cc.)	1820	2100	
	Average (cc.)	**2040**	**3060**	**1700**

Following the practice of the earlier papers, the physical measurements and certain other statistics are presented in Table

II. If the values tabulated here be compared with those summaries given in the first endocrine paper (1), it will be noted that certain discrepancies appear. These derive from the fact that the two groups are not identical in composition, several doubtful or incomplete cases in the earlier series having been replaced by later and more definite cases or by subsequent completed studies on untreated cases whose earlier records were not complete. The trends exhibited by the first series are more definitely established by the present group.

Fortuitously, the sex ratio in Groups I and II is the same, rendering the average values comparable. The average age of the Addison group is higher and the disease condition more severe (all of the patients have died during the past year) than with those having functional failures, of whom but one or two were probable incipient Addisonians. These differences are reflected in the several figures given above. The predominance of the females is certainly fortuitous, as the existing statistics indicate the reverse or, at most, a relative parity of incidence. We wish at this time to emphasize our consciousness of the limited number of data in this series, and the complete lack of warrant for any broad generalization. Only the paucity of similar reports in the literature and the necessity of considering adrenal

TABLE III

"VITAL CAPACITY" COMPARISONS

Observation		I	II	III
Weight	High (kgm.)	+10	+17	
	Low (kgm.)	—31	—36	
	% above normal	33	22	
	Average (kgm.)	**+10**	**+15**	
	% below normal	67	78	
	Average (kgm.)	**—21**	**—15**	
	*Total avg. (kgm.)	**—11**	**—8**	**—3**
Chest	High (cm.)	—4	+15	
	Low (cm.)	—10	—17	
	% above normal	0	33	
	Average (cm.)	—	**+8**	
	% below normal	100	67	
	Average (cm.)	**—7**	**—13**	
	*Total avg. (cm.)	**—7**	**—5**	**—2**
Lung Volume	High (cc.)	—29	±0	
	Low (cc.)	—51	—29	
	% above normal	0	0	
	Average (cc.)	—	—	
	% below normal	100	100	
	Average (cc.)	**—47**	**—14**	
	*Total avg. (cc.)	**—47**	**—14**	—

*Weighted for number of cases.

conditions as an integral part of any general method dealing with the endocrine glands leads us to present this compilation. The rarity of the condition—less than one-half per cent in our series of cases originally selected on the basis of probable endocrinopathy—means the lapse of a considerable time before an adequate number of observations could be available. As acutely conscious as the reader, of the limitations of this report, we offer it as a first approximation and as indicating tendencies only and not defining limits. The ages are similar to those of the other endocrine groups. The one child (III), a girl of seven, will be discussed later in the body of the paper. The heights are in no way remarkable nor indeed are the other values determined by the bony structure. The Sitting Height-Chest Ratio exceeds that which would be determined if only women were considered, and indicates probably that degree of emaciation which subsequent comparisons disclose. Taking Dreyer's (16) figures as the best available, the normal male ratio would be 1.053, the female 1.152 or, weighting for relative representation, the normal value would be 1.119. Group I gives the value 1.184, and Group II the slightly lower value of 1.173. The weight averages are below those recorded in the other endocrine groups. The average lung capacities of Groups I and II reflect the degree of asthenia incident to the progress of the disease. Interestingly, that for Group II compares favorably with the group averages of the other endocrine series.

As previously noted, the absolute data frequently are less informative than comparisons with so-called normal standards. Following our earlier practice these may next be considered.

Applying the comparisons with the Dreyer and West standards, as described in the earlier papers, it is obvious that while a few of the cases were overweight, the majority fell below prediction and the net average was actually 11 per cent for Group I and 8 per cent for Group II below that calculated. In passing, it may be said that in our entire series of studies this gland is the only one determining a negative average. The loss in predicted lung volume is of very significant magnitude in Group I but, oddly enough, considering the asthenia characteristic of these cases, in Group II is somewhat less in amount than that observed with the other endocrine glands. The elimination of obesity, in this group, another depressing factor of predicted lung volume, may explain the observation.

Certain of the observations, where the urine was the material examined, are collected in the next table.

The individual volume and specific gravity values show fluctuations analogous to those of the other series; the average of Group I shows a lowered kidney permeability, while that of Group II equates well with normal findings. The incidence of an albuminuria in 100 per cent of the cases, with casts in significant amount in one-half, offers a significant datum. Further, the presence of glycosuria in over 40 per cent of the cases raises a question that will be considered in detail under the caption of "carbohydrate tolerance." From the standpoint of differential diagnosis, the absence of "urobilinogen" is noted. Others have noted both increases and decreases in normal urine pigment, and McMann (17) has recorded a single instance of the presence of a foreign pigment. The 'phthalein test would seem to indicate a somewhat lowered kidney permeability, but the extraneous factors influencing this test limit its authority. The provocative urea curve, on the other hand, is most suggestive and corresponds well with the other evidences of kidney disease. In comparison with the groups of the other endocrinopathies and with a large

TABLE IV

Urine Data

Observation		I	II	III
Volume	Average (cc.)	750	1240	480
Specific Gravity	Average	1.011	1.016	1.007
Albumin	Positive (%)	100	100	100
Casts	Positive (%)	67	44	0
Sugar	Positive (%)	67	33	0
Urobilinogen	Positive (%)	0	0	0
Salol	Average (min.)	70	79	75
Urea Curve	Normal (%)	33	*14	—
	Low (%)	67	*86	—
Phenol-sulphone-Phthalein, 2-hour elimination	Average (%)	53	47	53

*Test not applied to two cases.

non-endocrine group (some fourteen hundred cases in all), we find that a low curve of elimination is shown in about 20 per cent as contrasted with the 80 per cent here observed. The Salol index is a high average value, indicating in the present instance rather the lowered renal permeability than an impaired gastric motility. The partition analysis of urinary nitrogen offers additional information. In the earlier papers we have shown that an increase in the so-called residual nitrogen fraction is of frequent occurrence in all endocrine and certain non-endocrine conditions.

TABLE V

Nitrogen Partition

Observation	I	II	III
Total Nitrogen....................(gms.)	6.43	7.81	2.31
Urea Nitrogen......................(%)	79.5	77.6	78.8
Uric Acid Nitrogen..................(%)	1.5	2.1	3.5
Ammonia Nitrogen...................(%)	4.3	5.4	4.3
Creatinin Nitrogen..................(%)	4.5	4.7	1.4
Residual Nitrogen...................(%)	10.2	10.2	12.0
% of cases with residual = or over 9%.....	33	67	100

Further, one of us (18) has demonstrated that this increase is ascribable, in part, to the presence in abnormal amount of substances usually occurring in but very small quantities. In addition, however, there remains a moiety which is unaccounted for by the increase of known constituents and which patently must be referable to the presence of unknown nitrogen containing substances. We shall touch on this point again in the consideration of the blood chemistry. Several other observers have recorded either the presence of increased amounts of normal or the appearance of abnormal constituents, but the contradictory opinions seem to exist about these as well as the general protein metabolism. Our figures show an average for the series superior to the established normal, exceeded only by that for thyroid and with more than half of the cases exhibiting significant increase above normal. The percentage values of the several other constituents accord well with accepted standards. The absolute nitrogen elimination is, however, significantly low. Reference to the composite group of the other endocrinopathies already mentioned shows an average of substantially 9 grams as against the adrenal value 17 per cent lower. Since these figures were derived from a study of the urine nitrogen partition alone, and not from protein metabolism experiments, no inference can be drawn as to retention. The patients were observed under the same conditions of liberal varied diet as were the other members of the series. That they show a characteristically lower nitrogen elimination for whatever cause, and that the partition formula departs from normality, may be regarded as indicated.

The results from the determination of certain blood constituents are given in Table VI.

TABLE VI

Blood Chemistry

Observation	I	II	III
Non-Protein Nitrogen (mgm.)	**42**	**37**	**34**
% over 35 mgm.	100	44	0
Urea Nitrogen (mgm.)	**17**	**16**	**11**
% over 17 mgm.	33	22	0
Uric Acid (mgm.)	**3.4**	**3.6**	**3.3**
% =or over 4 mgm. (net)*	0	11	0
Creatinin (mgm.)	**1.5**	**1.5**	**1.5**
Residual Nitrogen (mgm.)	**23.3**	**19.2**	**21.3**
Sugar (mgm.)	**86**	**88**	**†112**
% under 80 mgm.	33	22	0

*All demonstrated cases of nephritis deducted.
†Value doubtful from emotional element.

The non-protein nitrogen shows an average level distinctly in excess of the usually accepted normal, the more strikingly as the urine indicates a low level of protein metabolism. Blood urea, on the other hand, is a high normal, while blood creatinin and the average uric acid concentration is normal, the latter in spite of the presence of the several cases of nephritis. Similar findings have been recorded in experimental animals, though again a word of caution must be expressed as to the interpretation of results with the moribund subjects of acute experiments. Blood chemistry values are profoundly influenced by the fatal experimental conditions. In the work of Marshall and Davis (19) certain observations would not seem to be affected by this objection. In our own cases representing the chronic as opposed to the acute condition, the non-protein nitrogen and uric acid in many of them indicate the characteristic relations of early nephritis first reported by Chace and Myers (29). The point of greatest significance is found in the residual or undetermined fraction. The average value here far exceeds the usual normal limits assigned by convention (15±2 mgm.), and is even more marked in relation to our other groups.

It will be remembered in the discussion of the urine findings that the residual nitrogen fraction was found to be increased above the normal level. It was pointed out that this condition was not peculiar to adrenal involvement (the thyroid exhibits the anomaly in even more striking degree), but was shown generally in all endocrine and a fairly large group of non-endocrine disorders. As we see it, the observation rests upon an end result of a rather wide range of metabolic disturbances, and is, at present, wholly non-specific. That the composition of the increment is a constant either qualitatively or, in relation to individual components, quantitatively, is hardly to be conjectured. Rather it is a single observation summating a large number of individual aberrations into a seemingly common end result. Further study on the character of this fraction and the variation of the amounts of individual ocmponents, may prove to be of real diagnostic import. While the urine findings present an outward general unity, the blood in the adrenal cases offers a definite difference from the other endocrine entities. The blood of decapsulated animals has been frequently demonstrated to possess an inherent toxicity [Levin (21)]. This could arise from either of two causes, i.e., failure to remove poisonous wastes normally detoxicated by the gland, or synthesis of toxic materials as the result

TABLE VII

Residual Nitrogen in Blood

Non-Endocrine	(500 cases)	15.2 mgm.
Pituitary	(400 cases)	15.1 "
Thyroid	(200 cases)	15.2 "
Gonad (Ovary)	(200 cases)	15.3 "

of disturbed metabolism resulting from ablation of the adrenals. A third alternative, lowered resistance, would not necessarily connote a change in blood composition. The present observation could be adduced to support either of the first two explanations. With our present ignorance of the complete composition of that fraction of blood nitrogen in health, it is impossible at the present time to hazard even a reasonable speculation. As Folin has emphasized, the determination of the qualitative and quantitative composition of this moiety of the blood constituents offers great possibilities, both to the physiologist and the diagnostician.

The remaining observation, that of blood sugar, is also of great interest. That hypoglycemia occurs both in Addison's disease and with decapsulated animals, has been frequently recorded. In passing it may be said that the recording of blood sugar levels far below the convulsive threshold does not excite unlimited confidence in the actual numerical values. Low blood sugar, however, has come to have an accepted diagnostic value, and reference is frequently made to it. In the present series, the average is much lower than for any of the other endocrine groups, and in 25 per cent of the cases fell below the conventional normal lower limit of 80 milligrams.* This fact, like the incidence of glycosuria already recorded, will be considered later under the general carbohydrate tolerance.

The study of the form elements of the blood (Table VIII) yields results that in the main harmonize with current thought. While a variety of abnormalities are recorded in the literature, they are largely mutually contradictory. A secondary anaemia in the later stages and a more or less established lymphocytosis are the sole points of common agreement. The latter finding appears in our observations most strikingly in Group I; the former is missing from Group II as these cases were not in the terminal phase at the time of study. We observe a slight upward tendency of the eosinophilic elements, as has been recorded by others, although the point is one of those of debate. The picture, on the whole, is one of normality, barring the lymphocytosis and the anaemia of the Addisonians. The serological tests were uniformly negative.

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*This statement does not take cognizance of the lower levels produced by the progressively more refined methods recently published by Benedict (22) and by Folin (23). Both writers agree that the lowest figures obtainable by a dependable method give the truest picture of the actual blood sugar level. As all of the measurements here reported were made by the well known Folin-Wu method, only standards based upon it may serve as criteria. The relative values remain unaltered.

TABLE VIII

BLOOD MORPHOLOGY

Observation	I	II	III
Haemoglobin........................(%)	**77**	**87**	**85**
Erythrocytes.................(1,000,000)	**3.84**	**4.65**	**4.84**
Color Index...........................	1.0	0.93	0.88
Leucocytes.....................(1,000)	**6.9**	**7.9**	**6.3**

DIFFERENTIAL COUNT

P. M. Neutrophiles..................(%) % =or over 75%......................	**31** 0	**59** 11	**65** 0
Lymphocytes........................(%) % =or over 33%......................	**61** 100	**33** 33	**30** 0
Eosinophiles........................(%) % =or over 3% (net)*................	**2** 33	**2** 22	**5** 100
Endothelial Leucocytes..............(%)	**6**	**6**	**0**

*All cases deducted which present non-endocrine causes of eosinophilia.

In the next table will be found the results of the respiratory metabolism studies and certain concomitant observations.

The general consensus of opinion would seem to indicate that adrenal failure determines a downward tendency to the basal metabolic rate. Exceptions to this have been noted,* but in the main, dependable data show decrease which in some cases, at least [Muirhead (24)], assumes a very tangible magnitude. The animal experiments recording the converse of this were in some cases at least not controlled for superimposed effects, such as movement. Conceivably, the species also might play some part. The calorigenic action of adrenalin has been measured by Boothby and Sandiford (25) and their interpretations are confirmed by Graefe (26) in his recent monograph. This latter observation does not implicitly settle the question, since two glands are involved, but certainly does not negative a drop in basal rate from lowered adrenal function. In our own series the values ranged from —5 per cent* to —32 per cent; the net average (12 cases) being —17 per cent. Following the general method of presentation of Boothby and Sandiford, we have 4 between ±0 and —10 per cent, 4 between —11 per cent, and —20 per cent, 2 between —21 per cent and —30 per cent, and 1 below —30 per cent. As stated in the table, one case was omitted. The patient was a psychoneurotic woman, very restless and unable fully to coöperate. Several measurements were made, the best being 4 per cent above prediction, but this test was unsatisfactory and the observed rate significantly above the truth. Several of the other cases were probably not basal, and one had a slightly febrile temperature. As with the gonad cases where a similar inhibiting condition obtains, the values secured have been reported as they are representative of the results obtained with this group of patients. In the main it may be said that the severity of the condition is reflected in some measure in the degree of depression of the basal rate. This is not rigorously

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*Boothby and Sandiford (4) in their series showed one case with a rate above +20 per cent, while nine were within the normal range, only three falling below —10 per cent.

TABLE IX

Respiratory Metabolism

Observation	I	II	III
Basal Metabolism*			
Deviation........High............(%)	—10	†—5	
Low............(%)	—21	—32	
% below prediction	100	100	
Average	**—17**	**—15**	**—29**
% between +10% and —10%	0	33	
% =or below —10%	100	67	100
Temperature.......Avg............(deg.)	**98.1**	**97.9**	**98.8**
Blood Pressure			
Systolic.........Avg...........(mm.)	**90**	**‡96**	**90**
% =or under 110 mm.	100	89	100
Diastolic.........Avg...........(mm.)	**54**	**‡59**	**52**
% =or under 65 mm.	100	89	100
Pulse.............Avg........(per min.)	**75**	**74**	**94**
Respiration........Avg........(per min.)	**16**	**13**	**27**
Alveolar Carbon Dioxide............(mm.)	**38**	**36**	**34**
% under 40 mm.	100	100	100

*One case (psychoneurotic) omitted from Group II. See text.
†Febrile temperature 99.1°.
‡One case with long-standing cardio-renal disease and slight hypertension omitted.

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*Average of comparisons with both Harris-Benedict and Aub-duBois predictions.

true, however, as the asthenia leads to a nervous instability and to restlessness.

The characteristic hypotension recorded by many others is here definitely present. The average systolic falls below 100 mm. and individual observations of less than 90 are recorded. The slightly increased pulse is not clearly displayed, but again this may be referable to the phase of the disease represented. Certainly the average indicates no downward tendency. The respiration rate confirms the conclusion offered above, as the lowered rate is observed only in the terminal phase.

We did not observe the hypothermia which is said to be characteristic of the condition. A temperature of 97° F. is the lowest recorded in the series, while one is slightly above 99°.

Alveolar carbon dioxide is a low normal. This is probably more apparent than real, as the asthenia of the condition makes it difficult to secure a really representative sample. The value recorded is undoubtedly a minimum, but equally, is probably representative.

The last observation to be recorded in this portion of the report is the Carbohydrate Tolerance (Table X).

The findings here are diametrically at odds with the usually expressed opinion on the influance of the adrenal on sugar toler-

TABLE X

Galactose Tolerance

Group	Normal	Observed	Deviation
I Addison's Disease			
B-133	**40**	**5**	**—87%**
B-325	**30**	**20**	**—33%**
B-977	**40**	**20**	**—50%**
			Average **—53%**
II "Hypo-Adrenalism"			
B-62	**40**	**50**	* **+25%**
B-144	**40**	**30**	**—25%**
B-155	**30**	**20**	**—33%**
B-182	**40**	**30**	**—25%**
B-323	**40**	**20**	**—50%**
B-421	**30**	**5**	**—83%**
B-440	**40**	**10**	**—75%**
B-505	**40**	**10**	**—75%**
B-567	**30**	**10**	**—66%**
			Average **—45%**
III Pubertas Praecox	**20**	**20**	± **0**

*See text.

ance. There is a particularly voluminous literature in this field, and all writers seem to concur in the opinion that adrenal failure produces an increase in the tolerance. The great majority of the studies from which this opinion derives, are based upon the influence of epinephrin injections on the level of blood sugar or, less frequently, on the appearance of glycosuria, procedures outside the range of this discussion. Of the very few studies which correspond with the present investigation, Eppinger, Falta, and Rüdinger (27), state that they found a very high tolerance for glucose in three cases of Addison's disease. Mussio-Fournier (28), examining the urine, found a high tolerance for glucose in one atypical case, while numerous writers have reported the low blood sugar curves which are interpreted as indicative of an increased assimilation limit. In only one paper, that by Forschbach and Severin (29) in which blood sugar curves were the criterion, has the writer been able to secure any evidence of a contrary observation. In this latter paper, one case of Addison's disease is reported with glycosuria after the test meal, while this case and one other show a significant rise to the blood sugar curve. The paper as a whole, however, does not inspire unreserved confidence in the accuracy either of the diagnoses or of the numerical data. Such sugar levels as 25 and 38 are so intrinsically improbable as to require substantiation.

In opposition to the general opinion, with but a single exception all the cases in this series showed a normal or depressed tolerance for galactose. Question as to diagnosis is answered by the fact that the low tolerances were exhibited by the subjects presenting the typical Addisonian syndrome subsequently verified at autopsy. The one subject showing a slightly raised tolerance (+25 per cent) had an advanced nephritic condition of long standing to which the anomalous finding might be attributable. That an apparent kidney disorder is frequently found in adrenal disease, the data of this series amply testify. The contradictory results of the other observers already cited may be due to a lessened kidney permeability, possibly to the fact that glucose and not galactose was the sugar exhibited, or equally to other and unknown causes. The frequently reported hypoglycaemia of adrenal failure has been confirmed in this series. It is possible that this might influence the so-called tolerance if the latter were determined solely by the shape of the blood sugar curve without observation of the urine changes. Sugar anomalies produced by epinephrin injection fall outside the scope of the present discussion, as presumably they involve a mechanism different from that operated by the simple oral administration of a dose of sugar. Confirming our findings in this matter is the independent observation earlier recorded of an incidence of glycosuria in nearly one-half of the cases in the series. When one remembers the blood sugar levels recorded, it is evident that something intrinsic in the condition has affected the entire carbohydrate metabolism and that to the end result of lessening power of the organism to utilize sugar. Parenthetically, the glycosurias noted above do not have to invoke the influence of a relatively foreign sugar for an explanation.

Patently, much more work must be done on a larger number of authentic cases to permit final judgment in the matter. As it now stands, we have observed, in a few definite cases of adrenal disease, a depression of the tolerance for galactose which assumes, as the table indicates, a magnitude almost equal to that conditioned by pituitary aberration. In conclusion, it may be said that the well known hyperglycaemic action of suprarenin injection may to some extent have influenced thought. If we regard our cases as of adrenal failure, our findings, superficially at least, are contrary to natural prediction. The dualistic nature of the gland may account for the findings. With our meager data we are unprepared, at this time, to do more than offer our findings as facts without further effort to explain existing seeming contradictions.

PART II

The clinical analysis of this small group of cases presents some difficulties. The child (Case C-16) is omitted entirely, since her case is not comparable to any of the others. A full protocol with discussion will be given later in the paper. Of the remaining twelve, three were clear-cut demonstrated cases of Addison's disease with pigmentation, six were seemingly functional failures, with half of them possibly incipient Addisonians, and the remaining three were of an even more doubtful adrenal etiology. As, in the main, they have conformed to the general picture defined by the more authentic cases, and further, as thorough study failed to disclose any other cause for their presenting difficulties, we have felt warranted in their inclusion.

The authors desire to repeat, perhaps redundantly, that they are acutely conscious of the short-comings of this series. Only the Addisonians are certainly cases of adrenal disease, and they are but three in number. Their several pictures are consistent in detail, however, and may be adopted as criteria for the discussion of the larger number of assumed functional cases. Consideration of these latter is felt to be permissible in view of the many serious observers who avoid a guileless acceptance of the more extreme synthetic correlations of speculative endocrinology and yet concede the possibility of a lowered functional activity of the adrenal glands. The existence of accessory medullary and cortical tissue in other portions of the body, with the possibility of local involvement, offers additional ground for conceiving such a condition to be possible.

One other point should be noted. With so brief a series as the present, statistical analysis is not highly significant. Agreement with the results of the more extensive surveys of others offers some slight support for the possible accuracy of the diagnosis; difference emphasizes only the limited amount of our material.

Without further preamble, we may undertake a brief clinical analysis of the cases.

The sex incidence of the disease is usually stated as equal or with a slightly greater frequency among females. In the subdivisions of the present series, the females are twice the number of males.

The ages can be presented in tabular form:

TABLE XI

AGE AND ONSET

Decade	*Number*
21-30	6
31-40	2
41-50	2
51-60	0
61-	2

On the whole these values are in harmony with the usual record which places the years from 20 to 40 as those of greatest frequency. Late cases are known, however, the disease having appeared after the age of 80 in a few of those reported. Our three Addisonians were respectively 32, 48, and 61 years of age.

The time of onset in these three cases varied from three to twelve months before admission to the Clinic, with an average of nine months. As all of them have since died, the duration of the disease is known. Subject B-133, the youngest, had been sick for about one year at the time of admission and died almost exactly three years later (see Protocol in Part III). Subject B-977 exhibited an acute condition which began three months before our contact and ended three months later. The third Addisonian had been ill for one year prior to admission and lived for three years and one month after our study.

Of the functional group, five had been ill for less than four years, and one each reported severally 5, 10, and 25 years' duration. The last of these, subject B-323, referred her condition to some trauma to the coccygeal region at that time.

The family histories were particularly irrelevant, only one patient reporting tuberculosis, and one malignant neoplasm in fairly close relatives. Two others reported diabetes, the only endocrine condition cited, in reasonably near relatives.

The previous illnesses can be presented best in tabular form.

TABLE XII

PREVIOUS DISEASES

Measles	11	92%
Whooping Cough	8	67%
Mumps	7	59%
Chicken-pox	7	59%
Influenza	5	42%
Pneumonia	2	17%
Trauma to Coccyx	2	17%

While none of the Addisonians had a previous history of tuberculosis, three of the functional group had positive histories of earlier involvement, and in two of the others it was probable although no active process could be demonstrated at the time of study.

Two of the patients in the second (functional) group had a history of some trauma to the coccygeal region, possibly significant in view of the accessory tissue normally found there.

Seven of the twelve had had one or more tosillectomies, a proportion in accord with the incidence of tonsil disease already noted in the other endocrinopathies.

The chief complaints, as presented by the patients, are instructive.

Asthenia was offered as a major difficulty by eleven, and the twelfth case gave it as a minor symptom. The three patients with Addison's disease all complained of their pigmentation, and four of the functional group exhibited pigment changes of lesser magnitude in the skin.

Five of the group reported nervous instability as a principal symptom, and all of them exhibited it in significant degree.

TABLE XIII

CHIEF COMPLAINTS

Asthenia	11
Pigmentation	3
Nervous Instability	5
Gastro-Intestinal Disorders	3
Pain	4

In this connection, a few words may be apposite in regard to the personality changes engendered by this disease. Analogous alterations have already been commented on in our papers on the thyroid and the gonads. While a psychical asthenia accompanies the physical fatigability, it does not determine an apathy in environmental reaction. Sufferers from Addison's disease are highly emotional, irritable, and the victims of apprehensions and needless worries. Perspective is lost on the affairs of life, and annoying or disconcerting trifles assume the magnitude of major calamities. Mental depression is noted much more frequently than the reverse. They differentiate, however, from the sullen truculency of the hypothyroid subject and the shrill self-insistence of victims of gonad failure.

Gastro-intestinal disorders were of primary importance to two, and in addition, six more complained of poor appetite, flatulency, and other evidences of impaired function. Five were constipated, and one had persistent diarrhoea.

Pain was a common finding, and in four assumed major importance. It was rarely delimited as to site, but was usually found in the abdomen in every case as well as in other portions of the body.

The asthenia, pigmentation, and gastro-intestinal symptoms are frequently referred to as the triad of cardinal symptoms, while the other two are of usual occurrence. The frequency of representation of them in this group lends some support for the diagnosis in the assumed functional cases. While they may all derive from numerous other causes, some of these latter had been excluded by other parts of the study. Further, the symptom complex was but one evidence among the many, by the integration of which the diagnosis was established. We have already emphasized the necessity of regarding each diagnostic factor as significant only in its correlation with the general picture made up of many other independent measurements and observations. The agreement of our findings with those generally accepted as significant of adrenal disease, does not establish a diagnosis, but adds supporting evidence to the possible accuracy of our interpretation.

The majority of the patients showed an excessive susceptibility to infections of the respiratory tract, as shown by the data already recorded and by the fact that half of them reported very frequent colds (4), coryza (4), sore-throat (5), and kindred conditions.

Several of the group were subject to vertigo, and a number gave a history of fainting spells. Five complained of frequent and severe headache. Several had had otitis media in earlier years, and two showed a definite impairment of hearing. Nocturia was noted in 50 per cent, and intermittent polyuria in two patients. In the previous section the objective evidences of kidney involvement has already been emphasized. A true nephritis would seem to be even more frequently an accompaniment of adrenal disease than is the lowered permeability simulating nephritis of the thyroid failure.

The menstrual history of the eight women shows a relative normality.

TABLE XIV

MENSTRUATION

	Amount		
	Increased	*Normal*	*Diminished*
Irregular 3	1	0	2
Regular 5	0	4	1
Total	1	4	3

All of those showing irregularity had an increase in the interval, and with those of the entire group where the flow was not normal, the tendency was toward diminution. This is in harmony with the usual record of lowered exocrine activity of the gonads in adrenal disease.

A second supporting, if indirect, evidence is found in the marital histories of the group.

Only three of the twelve were married, two women respectively five and seven years, and one man whose married life extended over nearly forty years. Each of these unions had been productive of but one child, and there was no history of miscarriages. The direct data on libido were too meager to be significant, but the record given above may be regarded as possibly suggestive. In all of the other endocrine groups, including that of the gonad failures, the percentage of marriages is very much greater.

The physical examination yielded relatively few significant data.

Loss of weight and emaciation are usually predicated for adrenal disease. Three of our twelve patients were above their predicted weight, and of these one was the Addisonian in whom the disease ran a rapid course. This latter fact probably accounts for the anomaly. She was underweight at the time of her death. The remaining nine were all below their predicted weights, although three of them were still within the conventional normal limit of —10 per cent. The six remaining subjects averaged 22 per cent below their normal weight, and one of these (not an Addisonian) was 36 per cent below the calculated normal.

As has been noted above, 59 per cent of the group were pigmented in a greater or less degree. Several of the remainder were sallow, and only one exihibited a really healthy color of the skin. This was the patient (Case B-144) who was one of the doubtful group.

The hair presented nothing remarkable, there being no instance of a recognized deepening of color or marked anomaly in amount or distribution. Five of the patients had frankly poor teeth, and the dentition of several others was in but fair condition. As already noted, some patients had had tonsil operations; the tonsils of the remainder were normal.

One female patient had a slight thyroid enlargement; at the time of examination none exhibited adenopathy, though several had an earlier history of enlarged glands. Four patients gave evidence of past or present pulmonary disease, and three showed abdominal tenderness. Five exhibited diminished reflexes. The remaining features of the examinations were not substantially significant.

Of the special examinations but few excite comment. Four of the patients gave evidence of apparently earlier pulmonary disease and the pyelograms of two of the Addisonians showed destruction in the upper portion of the kidney.

The eye examination demonstrated 75 per cent to have enlarged blind spots, but only 25 per cent showed yellowish discs. In only one case was there a significant contraction of the fields, and this was in one eye, the patient suffering from iritis in the other.

Neurological examinations confirmed the findings of the routine report, while none of the other observations threw light on the potential endocrine condition.

In the main it may be said that the members of the functional group gave pictures varying in degree rather than in kind of involvement from those of the Addisonians. As has been noted, the three established cases of Addison's disease differed from each other in certain respects, as one would naturally anticipate, and the majority of the functional cases showed no greater variation from conventional standards. No attempt has been made to review the literature, as the few points of note in the clinical picture of this rare condition are matters of too general agreement to require debate.

Following the practice of the earlier papers in this series, the next section will be devoted to presenting the individual details of certain of the more representative and interesting cases in the form of protocols.

PART III

CASE PROTOCOLS

The significant laboratory data of the first group are given in tabular form.

CASE B-133. (CHRONIC) The patient's chief complaint was of pigmentation of the skin coupled with a marked asthenia. Since early childhood, she had presented several dark brownish moles on the face and a large irregular naevus-like dark pigmented area on the lower anterior half of the left side of the neck. Two years previously she noted an increase in the number of moles on her face, and one year previously a general darkening of the skin, most pronounced on the face, hands, and a band surrounding the middle of the body. The asthenia she dated from an attack of the grippe about a year previously, so that the pigmentation and weakness showed substantially the same chronology.

Family History: The father died at the age of 38 of diabetes. There were three living sisters and three others who had died in childhood of acute infections.

Past History: The patient reported the minor ailments of childhood, tonsillitis every year until a tonsillectomy six years earlier, and in addition, the attack of grippe already mentioned. She had had no association of which she was aware with tuberculosis. The other significant points in the history were abscessed ears ten years previously, teeth requiring much dental attention, and an occasional gastrointestinal disturbance characterized by flatulency, distress, and nausea. She had had occasional fainting spells, and at times numbness and tingling in the hands. The patient was unmarried, established the catamenia at the age of 14, and gave an entirely normal menstrual history.

Physical Examination: She was a fairly well developed, poorly nourished woman, 32 years of age. The exposed surfaces showed a peculiar copper colored appearance which during the examination was also observed in a broad irregular girdle about the waist. The other portions of the body were also brownish but less strongly pigmented. The naevus on the neck was remarked, and numerous brown moles on face, neck, and arms. The lips were somewhat pigmented, as were the gums and small areas of the buccal mucosa. Examination of the lungs showed a questionable increase in intensity of the breath sounds at the left apex, and a few dry rales heard throughout both lungs. There was slight tenderness in both costal vertebral angles, a fine tremor of the hands, and a bluish color of the nails. No evidence of cardiovascular disease was detected.

Laboratory Summary: The urine volume was somewhat high; there was a trace of albumin. The elimination was excellent, the protein intake ample, and the partition formula normal. The blood morphology was normal except for a marked lymphocytosis. The blood showed an increase above the normal of all of the nitrogenous constituents, and a blood sugar at the low level of the normal. The vital capacity measurements showed the patient to be 8 per cent underweight, and with a significant loss from the predicted lung volume. The basal rate was recorded as —6 per cent, with low blood pressure, rapid pulse, and slightly sub-normal temperature.

TABLE XV.

ADDISON'S DISEASE
GROUP I. ADDISON'S DISEASE.

Observation				
Case Number		B-133		B-977
Date	Jan., 1924	Feb., 1924	May, 1924	April, 1928
Interval (mos.)	—	1	3	—
Sex	F	F	F	F
Age (yrs.)	32	32	32	48
Height (cm.)	162	162	162	158
Weight (kgm.)	51.8	50.2	50.0	61.4
Weight Deviation (%)	—8	—11	—11	+10
Lung Volume Deviation (%)	—28	—29	—28	—42
Basal Rate Deviation (%)	—6	—10	—13	—21
Blood Pressure (mm.)	104/62	90/54	108/70	90/58
Pulse (per min.)	94	74	76	86
Temperature (deg. F.)	97.2	98.4	97.6	97.1
Alveolar CO_2 (mm.)	31	35	36	40
Urine Volume (cc.)	2150	730	1800	720
Specific Gravity	1.013	1.025	1.015	1.014
Albumin	+	+	0	+
Casts	0	+	0	+
Sugar	0	+	0	0
Total Nitrogen (gms.)	13.58	8.37	15.13	6.13
Residual Nitrogen (%)	2.4	7.1	11.2	7.2
P. S. P. 2-hour Elimination (%)	79	62	—	42
Non-Protein Nitrogen (mgm.)	40	39	42	43
Uric Acid (mgm.)	4.3	3.4	4.2	3.5
Sugar (mgm.)	80	75	80	99
Haemoglobin (%)	90	85	90	75
Erythrocytes (1,000,000)	5.52	4.28	4.61	3.81
Color Index	0.82	0.99	0.98	0.98
Leucocytes (1,000)	8.2	8.7	6.8	8.3
Neutrophiles (%)	45	17	33	39
Lymphocytes (%)	42	73	59	50
Eosinophiles (%)	1	4	2	3
Endothelials (%)	12	6	6	8
Misc. (%)	0	0	0	0
Galactose... Normal (gms.)	40	40	40	40
Observed (gms.)	—	5	—	20
Deviation (%)	—	—87	—	—50

This value of the basal rate was not regarded as accurate since the patient was slightly nervous.

Radiography of the chest give normal findings, but an indefinite shadow was remarked above the upper pole of the left kidney.

Skin Examination: The observer at this time commented on the suggestion of Addison's disease, felt that mineral poisons and a chloasma of toxic origin must also be considered, and recommended a biopsy.

Discussion: Feeling that the observations available were too limited to warrant a final diagnosis, and desiring to study the patient more thoroughly in the hope of resolving the condition, she was admitted to the Hospital a few weeks later and a much more complete study was undertaken. The interval history was irrelevant.

Second Examination: The urine volumes were found to be somewhat low, and the urine contained albumin, sugar, and granular casts. Her protein intake had decreased although it was still above a maintenance level. The residual nitrogen fraction showed a definite upward tendency although still within the conventional normal limit. The blood showed a marked increase in the lymphocytes and a 4 per cent eosinophilia. There was evidence, for the first time, of a slight degree of anaemia, with a color index of one. The blood chemistry values were somewhat lower for the uric acid, the high non-protein nitrogen remained unchanged, while the blood sugar had sunk below the conventional normal limit. The 'phthalein test, though still normal, had fallen off somewhat. The patient had lost 1.6 kgm. weight. The lung capacity was substantially unchanged. The basal rate was 10 per cent below prediction, and again the measurement of the observed rate was undoubtedly somewhat above the truth. A sugar tolerance test was performed with galactose, and it was found that the assimilation limit was greatly depressed, even so small a dosage as 5 grams being enough to produce a transitory appearance of galactose in the urine. The alveolar carbon dioxide was still low, an observation ascribed in part to the patient's weakness, with consequent difficulty in collecting a representative sample.

Neurological Examination gave entirely normal findings throughout.

Pelvic Examination gave normal findings.

Radiography: The skull and sella were normal. An area of calcification in the falx cerebri was reported. The chest was negative, and the radiogram of the abdomen failed to confirm the shadow near the kidney which had been previously recorded. Some density of the right mastoid cells was noted, the sinuses were otherwise normal.

Eye Examination: The discs were yellowish in color, the blind spots slightly enlarged; the remaining findings were normal.

Urea Curve: The data showed a depressed elimination, both qualitatively and quantitatively.

Biopsy: A biopsy was performed and the excised tissue was subjected to careful examination by Dr. A. M. Greenwood. The portion from the naevus was reported by him as characteristic of the tissue from which it was taken. The second section, which was excised from another part of the neck, showed only increased pigment in the basal layer, which, with special staining, was demonstrated to be melanin.

Discussion: The patient's history and her presenting symptoms were naturally suggestive of Addison's disease. There were further in the literature a few records of lowered basal rate in this condition in man, perhaps the most significant of which were the records of Muirhead (24) from the Mayo Clinic, and those of Aub (30) and his associates. The reports from several laboratories of increased basal rate in experimental animals with injury to these glands was not regarded as significant since the animals were not in a basal state. On the other hand the injection of adrenalin is known to increase the respiratory metabolism. The patient's sugar tolerance represented a sharp divergence from the few existing records in the literature. This has already been discussed earlier in the paper. The patient presented evidence of lowered kidney permability, the low blood pressure and blood sugar generally associated with Addison's disease; certain of the other possibilities such as primary anaemia and bronzed diabetes were practically eliminated by certain of the other observations. On this basis a tentative diagnosis of Addison's disease was established and medication instituted.

The clinical features of particular interest were the absence of demonstrable foci of tuberculosis elsewhere in the body, the albumin and casts in the urine, the evidences of depressed renal function furnished by the blood chemistry, phenolsulphonphthalein test, and urea curve, and the character of the asthenia.

The impression still persists that non-pulmonary tuberculosis is practically always associated with the pulmonary form, and that a diagnosis of non-pulmonary tuberculosis rests on insufficient evidence if the former is not demonstrable. While it is true that autopsy usually shows some evidence of pulmonary involvement in those patients exhibiting the disease elsewhere, it is more often than not impossible to demonstrate the association clinically. Therefore absence of pulmonary tuberculosis demonstrable by clinical methods should not deter one from making the diagnosis of the disease elsewhere in the body.

Albumin and casts were present in the urine of the majority of our patients with Addison's disease, and were generally accompanied by other evidences of disturbed renal function. (See table XV.) Such findings, generally significant of nephritis, should not be allowed to direct one's attention away from possible adrenal disease if they are accompanied by significant hypotension and asthenia of the characteristic type. If pigmentation is present there is little danger of this, but if there is no pigmentation, as happens, according to Falta (9), in nearly one-third of the cases, undue emphasis upon the urinary findings may decoy one away from the true diagnosis.

The character of the asthenia in our patients with Addison's disease has been so typical that its main features seem worth emphasizing. Although there is usually complaint of constant lack of energy, the feature peculiar to adrenal destruction has been the sharp exacerbation of weakness upon effort and its rather rapid remission when effort ceases. The patient under discussion furnished a clear example. She was a school teacher and was able to carry out most of her tasks without distress, although she was very weary when the day's work was over. An attempt to lead the class in a short and easy "setting up drill," however, would almost always produce a feeling of profound weakness, accompanied by dyspnoea, trembling, and frequently nausea. Ten or fifteen minutes rest would result in complete disappearance of this asthenic condition, leaving her "practically as good as she was before." This cycle of events which seems to lend supporting evidence to Cannon's emergency theory is, in our experience, typical of Addison's disease (if severe cardiac disease be excluded), and is of fundamental importance in distinguishing it clinically from other conditions causing asthenia.

In April the patient returned for a basal metabolism test which showed a level of —5 per cent under what seemed to be satisfactory conditions. The blood pressure had risen to 112, and the patient apparently was much improved. In May a series of observations was made (see table) which may be briefly reviewed.

The urine was again ample in volume, as in the beginning; albumin, sugar and casts had disappeared; the elimination was excellent. The appetite had improved, and the protein intake was almost double that of February. The residual nitrogen, however, had increased to a point significantly above the conventional normal. The blood still showed a marked lymphocytosis but definitely lower than that recorded in February, while the eosinophilia had returned to a normal value. Both the red count and the haemoglobin were somewhat increased, and there was no secondary anaemia. The blood sugar showed an increase to the initial low normal level. The nitrogenous constituents, however, had also increased to substantially their initial value. The patient's increased protein intake undoubtedly contributed something to this. The weight was substantially unchanged, as was the vital capacity. The basal rate was now 13 per cent below prediction, with the blood pressure slightly above that of the first record and significantly superior to that of the second.

Radiography: An x-ray plate taken at this time raised a question of a possible area of increased density in the mid-portion of the right wing of the sacrum.

The patient was continued under medication throughout the summer, and in the fall resumed her occupation which she had earlier been obliged to discontinue. She had gained three kilograms in weight. The blood pressure maintained the advantage shown, and her general condition showed a definite improvement.

The Muirhead treatment, modified as symptoms indicated, had been faithfully followed. But the patient was extremely sensitive to adrenalin, and its administration was omitted early since it seemed to do more harm than good. Cortical substance was, however, well tolerated, and the subjective symptoms became much less marked during its use. The patient carried on her work as a teacher with very little discomfort, and her "setting up drill" now rarely caused more than moderate fatigue. From time to time she had sudden attacks of abdominal pain and nausea, rarely causing vomiting, but on the whole her condition was excellent and her energy sufficient.

During the Christmas holidays of 1927 she caught cold. In spite of it she returned to work two days later. She showed no untoward effects from the "cold" when she started for school in the morning, but on reaching home in the afternoon she complained of the abdominal pain previously mentioned, and of difficulty in breathing. Her physician was summoned and found her in a state closely simulating surgical shock. The extremities were cold; pulse small, rapid, and feeble; breathing rapid, shallow and labored. No evidence of pneumonia could be found. She grew worse very rapidly. The breathing was described by her physician as being "like that of an overetherized patient," and it soon became necessary to hold the jaw forward to prevent strangulation. She became unconscious and died, apparently of respiratory failure, within eight hours after returning to her home, on foot.

We were fortunate in securing an autopsy and are indebted to Dr. Charles F. Branch for his skillful services in this connection. The skin over the entire body was of a peculiar dark brownish tinge, the lungs were normal except for a well defined edema, the liver gave evidence of recent parenchymatous degeneration, and the right ovary showed two small simple cysts on the upper surface.

Kidneys: Left: The approximate weight was 150 gms., it was firm, smooth, regular, and bright reddish-brown in color. The cut surface disclosed a normal relationship between the pyramids and cortex, the latter measuring about 6 mm. in width, the entire surface being markedly injected, and upon scraping yielding a slightly blood-tinged purulent material on the knife edge. The capsule stripped with ease, leaving a markedly injected surface. The pelvic epithelium was not injected. *Right:* Was similar in every respect to its fellow on the left. *Microscopic Examination:* Many of the tubules were completely desquamated, while in others the epithelium was swollen and coarsely granular; the cytoplasm and nucleus took a uniform pink stain. The lumens contained varying amounts of coagulated serum, epithelium and debris. The glomeruli were engorged and stained poorly. The vessels throughout were engorged; there was moderate general increase of connective tissue throughout which in places was infiltrated with, and showed accumulations of leucocytes. Occasional sclerosed glomeruli were noted. The connective tissue about the pelvis was edematous.

Adrenals: After diligent search in the region where the adrenals should have been, on either side was discovered some small compact masses of pale white tissue, seemingly fibrous in character, which were preserved as sclerosed adrenals. Upon examining the cut surfaces of these masses absolutely no evidence of any structure resembling adrenals was observed. *Microscopic Examination:* Absent on either side and apparently replaced by a mass of tissue which upon microscopical examination appeared to be enlarged sympathetic ganglia.

From the clinical standpoint the most interesting features of this case are the long duration of the disease after the diagnosis was established and the considerable improvement under treatment, which is astonishing in the light of the autopsy findings, and the character and brevity of the final stage, suggesting that a very small fraction of the total adrenal tissue may be sufficient to support life, but that even a mild infection may overwhelm the patient.

CASE B-977 (ACUTE). The patient's chief complaint was of a brown coloration of the skin, coupled with a marked degree of asthenia. Three months previously the patient's mother had died, the event producing a profound emotional shock. Following this she became very weak and began to lose weight rapidly. A few weeks later she found herself unable to continue her employment. She developed an attack of grippe, and during her convalescence noted that her skin was becoming brownish in color. During the three months of the course of her complaint she had lost 25 lbs. The weakness and pigmentation had both been progressive. Five days before admission she had had a single attack of vomiting without well defined cause.

Family History: The mother died following an operation for hernia at the age of 75, and the father at the same age of cerebral hemorrhage. The remaining family history was entirely irrelevant.

Past History: Beyond measles at three, diphtheria at 13, and a tonsil operation at 38, the patient's history was relatively uneventful. She had always been healthy and a steady worker. Her teeth had been removed for pyorrhea. She stated that a year and a half previously, after an attack of epigastric pain, a diagnosis was made of duodenal ulcer, and under medical advice she had been on a gland diet since that time. The menstrual history was entirely normal up to six months ago, but in this interval she had missed three periods. As the patient was 48 years of age she ascribed this to an approaching menopause. She reported a slight tingling sensation in the right hand occasionally, and a slight skin eruption on the arms after eating tomatoes. There had been no association with tuberculosis.

Physical Examination: The patient was a well-developed, well-nourished woman of 48. There was a bluish-brown pigmentation all over the body, most marked on the exposed surfaces. The patient was apathetic and appeared fatigued. There was apparently some loss of hearing in both ears. The buccal mucosa was pigmented, the chest apparently normal, the radial arteries were slightly firm. Routine neurological findings were substantially normal except for somewhat poor pass pointing.

Laboratory Summary: The urine was somewhat scanty and it contained albumin and a very few hyaline casts. The elimination was poor. The protein intake was below a maintenance level, and the residual nitrogen showed an upward tendency although within the conventional normal limit. The blood morphology showed a lowering of both haemoglobin and leucocytes, and a normal color index. There was a marked lymphocytosis and a 3 per cent eosinophilia. The blood non-protein and urea nitrogen values are definitely above the normal level, while the blood sugar was normal. The 'phthalein output was definitely low, and the urea index below the normal. The patient was 10 per cent overweight but nearly 50 per cent below her predicted lung volume, a finding probably referable to her asthenia. The basal rate was 12 per cent below prediction, with definitely low blood pressure, and, at the time of the test, a somewhat rapid pulse. Later evidences seemed to indicate that the basal rate, as recorded, was probably distinctly above the truth, and that the real rate was between 20 per cent and 30 per cent below prediction. The value recorded in the table, derived from a second test, was —21 per cent, and this was still probably somewhat high. The patient's sugar tolerance was half the normal level.

Chest Examination gave no evidence of disease.

Endermal Skin Tests gave no evidence of protein sensitivity.

Liver Function (McClure) determination indicated normal biliary function.

Orthopedic Examination: Moderately pronated feet were the only abnormality recorded.

Skin Examination: The appearance was regarded by the examiner as typical of Addison's disease.

Radiography: A series of gastro-intestinal plates showed a constant defect consistent with duodenal ulcer. There was some degree of visceroptosis. The skull and sella were normal, heart and lungs normal, and a plate of the lower leg where the patient had a tender spot showed no abnormality.

Cardiogram gave normal findings except for a relatively low voltage consistent with the patient's adynamic state.

Audiogram showed normal hearing.

Cystoscopic Examination gave normal findings.

Eye Examination: The discs were yellow and the fundi showed slight vascular sclerosis and a generalized tessellated pigmentation.

Urea Curve: Was normal in shape and gave evidence of good elimination.

Levulose Tolerance was much depressed.

Icteric Index and Van den Bergh reactions indicated normal function.

Pyelograms: The right renal pelvis was dilated; the calyces blunted. The left kidney was of the spider type.

Discussion: The whole general picture here was felt to be consistent with Addison's disease in a somewhat acute state. The lowered sugar tolerance, while not in accord with other reports in the literature, was consistent with our own observation. The Muirhead treatment was initiated, the patient remaining under observation in the Hospital. One month after beginning treatment a satisfactory basal rate showed a level only 4 per cent below prediction, with distinctly low blood pressure (88/52) and a slightly rapid pulse. The patient's condition did not improve, however; the asthenia was progressive and complicated by sensations of pain which were not exactly localized but seemed to be confined to the body. Toward the end of the second month the patient's failure became more rapid, and early in the third month after admission, death supervened. An autopsy, the details of which we owe to the courtesy of Dr. Charles F. Branch, showed bilateral pulmonary tuberculosis and Addison's disease.

Adrenals: The left weighed 24 grams. It was slightly injected and had a distinctly firm, woody feel, was coarsely nodular and the surface, instead of showing the customary fine mottling of the cortex, was almost a uniform dull, pale yellow. The surface showed no normal landmarks remaining, the cortex and the medulla being completely absorbed in a coarsely mottled, yellow and reddish gray mass, with not infrequent small islands of calcification present. No caseous material was observed, per se, although many areas simulating it were seen with the naked eye. The adrenal of the opposite side was similar in every respect to its fellow on the left. *Microscopic Examination* showed that the normal histological architecture of the organ had been completely replaced by a mass of amorphous. caseous material. This was surrounded by a thick fibrous capsule, infiltrated with a large number of endothelial cells and lymphocytes.

Except to emphasize its similarity to the previous case, there is little to add from the clinical point of view. The picture of impaired renal function was similar to that already discussed. The bilateral pulmonary tuberculosis was obsolete. and gave no evidence of its presence by either roentgenologic or clinical methods of examination, supporting our previous statement that inability to demonstrate pulmonary tuberculosis during life is not an argument against the existence of a non-pulmonary infection.

GROUP II. "HYPOADRENALISM"

CASE B-421. The patient was a young man whose chief complaint was of constant glycosuria for the past five years, associated during the same interval with intermittent periods of profound fatigability. He was disposed to date the initial onset of his condition from an attack of influenza nearly 7 years previously, following which he had an attack of severe mental depression and a general slowing up of psychomotor activity. The condition passed in a few weeks but had recurred at intervals. Five years ago, following one of them, he consulted a physician who found several per cent of sugar in the urine. A diabetic diet improved his general physical condition but did not render him sugar free. Three years ago he entered a hospital and was put on a starvation diet for six weeks with a resulting loss of 40 pounds in weight. but again without rendering him sugar free. Throughout his entire period the attacks of mental and physical depression had recurred. usually lasting from one to two months and with a gradual recovery.

TABLE XVI

"HYPOADRENALISM"

Case Number	B-421	B-182	B-323	B-505	B-567	B-940
Sex	M	F	F	F	M	F
Age (yrs.)	22	22	40	26	25	68
Height (cm.)	175	163	165.5	154.5	165.5	160.5
Weight (kgm.)	64.1	34.8	60.6	41.8	52.0	51.8
Weight Deviation (%)	—6	—36	—1	—12	—3	—2
Lung Volume Deviation (%)	—8	—29	—2	—28	—15	—45
Basal Rate Deviation (%)	—32	—18	—18	—11*	—16	+5
Blood Pressure (mm.)	114/72	92/54	90/50	88/58	85/66	108/62
Pulse (per min.)	64	73	54	88	76	87
Temperature (deg. F.)	98.0	98.6	97.2	98.0	97.4	97.0
Alveolar CO_2 (mm.)	39	34	39	39	37	42
Urine Volume (cc.)	1450	1680	1050	540	610	400
Specific Gravity	1.039	1.005	1.013	1.025	1.020	1.020
Albumin	+	+	+	+	+	+
Casts	+	0	+	+	+	+
Sugar	30	0	0	0	+	+
Total Nitrogen (gms.)	14.73	4.24	7.29	6.02	5.70	4.92
Residual Nitrogen (%)	11.0	5.7	13.3	10.1	18.0	13.8
P. S. P. 2 hours (%)	61	26	48	35	55	26
Non-Protein Nitrogen (mgm.)	47	36	35	35	26	41
Uric Acid (mgm.)	4.8	2.9	3.6	3.3	2.0	5.3
Sugar (mgm.)	85	93	93	76	85	111
Galactose... Normal (gms.)	30	40	40	40	30	30
Observed (gms.)	10	30	20	†20	10	20
Deviation (%)	—67	—25	—50	—50	—67	—33
Haemoglobin (%)	100	95	70	70	80	75
Erythrocytes (1,000,000)	5.36	5.12	4.21	3.55	4.02	4.40
Color Index	.93	.93	.82	.99	1.00	.85
Leucocytes (1,000)	9.3	5.9	6.7	8.4	10.8	19.2
Neutrophiles (%)	58	58	75	62	58	82
Lymphocytes (%)	28	32	24	29	37	8
Eosinophiles (%)	3	0	1	2	2	0
Endothelials (%)	10	10	0	7	3	10
Misc. (%)	1	0	0	0	0	0

* True rate lower.
† Test incomplete. Tolerance possibly lower.

Family History: The mother had a renal disorder which had led to three therapeutic abortions after she had borne four children, of whom the patient was the third. All of the siblings had died in early infancy. Cases of tuberculosis, cancer, and diabetes were recorded in grandparents and great grandparents; none in the immediate generations.

Past History: The patient's birth history showed a normal delivery but a very long labor. Development was entirely normal. At the age of six he had measles, and this was followed by an abscess in the neck and what was said to be a spot in the lungs. The chest condition apparently cleared up in about two years. He further reported minor ailments, diphtheria at the age of nine, and a severe attack of influenza at 15 with a very slow convalescence. He grew very rapidly between the ages of 13 and 15. He also had a tonsillectomy at 14, and trauma to the head at the age of 8 which apparently produced only surface injury. The regional history showed frequent earaches in childhood, soft teeth requiring much dental attention, constipation, but was otherwise not remarkable. There was a history of a fairly active sex life with no venereal infection.

Physical Examination: The patient was a well developed and fairly well nourished young man of 22. His teeth showed much dental attention, the chest was normal; there was a slight tremor of the fingers, rather abundant hair growth of normal distribution, and somewhat hyperactive knee jerks.

Laboratory Summary: The urine volume was normal, elimination and balance good. An average content of 30 grams of glucose was reported; the remaining findings were normal. The nitrogen partition determination showed an adequate protein intake and a high residual nitrogen fraction; the blood morphology was substantially normal; there was a marked increase in the level of the nitrogenous constituents, and a low normal blood sugar. The 'phthalein test and alveolar CO_2 were normal. The patient was 6 per cent underweight and of substantially normal lung capacity. The basal rate was 32 per cent below prediction, with normal blood pressure and slightly low pulse.

Adrenalin Test: Injection of adrenalin produced a definite increase in the blood sugar level from 82 to 122 mgm. with a gradual subsidence, the level being 100 mgm. at the end of two hours. There was a progressive leakage of sugar through the kidney.

Radiography: The skull and sella were entirely normal.

Neurological Examination: There was no evidence of organic nervous lesion. The examiner remarked that the pupils were widely dilated, and that after light stimulus there was a slight contraction followed by immediate dilatation.

Audiogram: Definite loss of hearing, except in the higher register, was noted.

Eye Examination: The blind spots were slightly enlarged. The findings were otherwise normal, the examiner failing to confirm the anomalous pupillary reaction noted above.

Discussion: The general picture here presented was in some measure consistent with a disturbance of each of two independent endocrine glands, namely, the adrenal and the pituitary. The basal rate was of the order of adrenal or thyroid failure, but the latter is practically excluded by the patient's sugar tests since no other evidence presented of any additional cause for his depressed tolerance. In hyperpituitary cases, hypertension, and evidences of hypertensive nephritis are not infrequently found, but they are associated with an over-activity of both lobes. While most adrenal cases present a markedly lowered blood pressure, we have seen one case with an associated kidney involvement which exhibited a hypertensive level. On the basis of the markedly lowered sugar tolerance, the definitely lowered basal rate, the suggestion of renal disturbance conveyed by the picture of the blood chemistry, the patient's general history, the unimpaired libido, and a number of other generally supporting evidences, it was felt that diagnosis of functional hypoadrenalism was warranted to the point at least of undertaking experimental medication.

We have been fortunate enough to keep this patient under supervision, and have had opportunities for checking certain of the laboratory findings at not infrequent intervals. During the year 1926 a number of such observations were made, but at the end of this time the patient had so far improved from the clinical standpoint that the frequent checks were omitted. Early in 1928 the patient reported and the improvement previously noted was found to have persisted. Certain of the more significant data can be reduced to tabular form and discussed independently.

TABLE XVI-a

RESPIRATORY METABOLISM

Date	B. M. (%)	B. P. (mm.)	T. (deg.)	Wt. (kgm.)	Dev. (%)
2-1-26	—32	114/72	98.0	64.1	—6
13-2-26	— 7	118/60	97.4	63.8	—7
1-7-26	—11	116/64	97.8	63.6	—7
26-10-26	—26	108/66	97.4	64.6	—6
11-12-26	—23	110/64	97.6	64.9	—5
21-3-28	—18	108/70	98.0	70.1	+2

Inspection of the table shows an improvement in the basal rate to a substantially normal level within the course of a few weeks, and this was maintained with but slight variation for another five months. Following this the summer vacation intervened, and in the fall the patient was found to have lost on the basal rate and to have slipped back nearly to his earlier level. That he had not been assiduous in following his treatment was freely acknowledged. The blood pressures follow the same general trend, the body weights remain fairly constant. Although medication was intermittent following the last test in 1926, the patient had gained in weight and improved somewhat in his basal level when seen in 1928.

The next table shows the changes in the blood chemistry, and here the improvement is very striking. The diminution in the residual nitrogen fraction to a sustained normal level is certainly significant. The rise of blood sugar during the early period of active treatment was also interesting. The blood uric acid was favorably affected as well, but at the time of the last examination it had returned to its original level. A few of the urine sugar values are given in the next table.

TABLE XVI-b

BLOOD CHEMISTRY

Values in mgm. per 100 cc. blood.

Date	N. P. N.	Urea N.	Uric Ac.	Creat.	Residual	Sugar
2-1-26	47	23	4.8	1.5	21.8	85
13-2-26	42	22	4.7	1.5	17.8	91
1-7-26	43	21	3.9	1.5	20.1	99
26-10-26	38	18	4.2	1.5	8.0	95
11-12-26	32	15	4.7	1.6	14.8	86
21-3-28	36	19	4.7	1.6	14.8	86

TABLE XVI-c

URINE DATA

Date	Vol. (cc.)	Sugar (gm.)
2-1-26	1450	30
1-7-26	1660	16.6
26-10-26	2550	74
11-12-26	1430	71.5
21-3-28	1620	70.6

The lowering of the sugar elimination and its return to a much higher level when dietary restrictions were removed, is obvious from the figures given.

During the period of observation in 1926 a cardiogram was secured which showed a normal organ.

Clinically, it is impossible to furnish sufficient supporting evidence for the diagnosis of "hypoadrenalism" in this case. It is even impossible to state what that evidence should be, since there exists no proven symptom pattern of the condition. There is no doubt, however, that the patient has a definite endocrine disturbance, and the more important symptoms coincide more nearly with those of adrenal impairment, as evidenced in early Addison's disease, than with any other condition known to us. The intermittence of the subjective symptoms is not consistent with the dead level of energy deficiency characterizing thyroid and pituitary deficiency. The undiminished libido would be an enormous stumbling block for any one desirous of explaining the picture on the basis of hypogonadism. The lack of neurological findings renders "piqure" diabetes improbable. And finally, the subjective and objective response to treatment is suggestive, though by no means convincing evidence, that the working hypothesis is correct. Similar responses to treatment have recently been reported by Koehler (31), but we do not share his belief that they can be regarded at present, as an adequate therapeutic test. We are reporting these cases of "hypoadrenalism" because it seems desirable to add to the evidence for or against such a condition rather than because we believe its existence proved.

CASE B-182. The patient's chief complaint was of fatigue and indigestion. She dated the latter from an attack of "ptomaine poisoning" which had occurred some 4 years previously, and which was characterized by abdominal pain, nausea, vomiting, and diarrhoea. Six months later the same group of gastrointestinal symptoms reappeared and had continued intermittently up to the time of her admission for the study. She had lost 17 pounds during this interval but had been underweight at the time of its onset. The condition had been accompanied by a marked fatigability which ultimately obliged her to discontinue her occupation, which was clerical in nature. At about the time that the symptoms began, brownish pigmented areas developed on the face. These have persisted although there has been some variation in their intensity.

Family History was irrelevant.

Past History: The patient reported minor ailments and influenza at the time of the epidemic. Some time after the onset of the present condition a gastrointestinal x-ray study was carried out which yielded only negative results. In spite of this the patient was placed on an ulcer diet for some time without improvement in her symptoms. She complained of an occasional headache, poor appetite, and flatulency. The menstrual history showed a normal onset, some irregularity with increase in the interval, and a very scanty flow over periods of seven days. Beyond an occasional ache in the lower limbs, the remaining history was entirely irrelevant.

Physical Examination: The patient was a poorly developed and distinctly emaciated girl of 22. A slight dullness at the apex of the right lung and increased vocal fremitus on the right side were reported. Pigmented areas were noted. The right knee jerk somewhat below the normal activity; the remaining findings were normal.

Laboratory Summary: The patient was 36 per cent underweight and had lost nearly one-third of her predicted lung volume. The basal rate was significantly below prediction, and the observed value was somewhat above the truth, as the patient's breathing was very irregular and the trend of the curve not exactly determined. A later measurement showed a value of about —23 per cent, and there was some doubt if this also were truly representative. The blood pressure was at a distinctly hypotensive level; the alveolar carbon dioxide below a normal level. The urine volume was ample but the elimination very poor. Albumin was recorded; no casts were observed. The protein intake was definitely below a maintenance level and this would undoubtedly tend to lower the observed basal rate. The blood nitrogen values were relatively high in view of the low level of protein metabolism. The blood sugar was normal; the sugar tolerance somewhat depressed; the blood morphology was substantially normal.

Radiography: A gastro-intestinal study showed ptosis of the stomach, but conditions otherwise normal. The skull was normal. The left lung showed fibrosis, apparently due to an old infection, while the right lung was normal.

Neurological findings were normal.

Pelvic findings were normal.

Eye Examination: The patient showed much enlarged blind spots but otherwise normal conditions.

Discussion: Viewed from the endocrine standpoint, the thyroid could be eliminated by both subjective and objective evidences. With a lowered sugar tolerance and basal rate there is a suggestion of pituitary dysfunction which the enlarged blind spots might be adduced to support. The relative degree, however, of abnormality in these two tests did not conform with the usual pituitary formula. The combination is likewise found with the gonad failure, and here the low alveolar carbon dioxide might be regarded as a supporting evidence. That this low level was in part due, however, to an inability of the patient, through asthenia, to perform the test properly, robs the actual level of something of its authority. With the patient's poor nutrition one would infer a tendency not to lower but to raise the sugar tolerance, on the basis of lack of saturation of the tissues in accordance with Folin's theory. We have observed such a change in under-nourished patients without endocrinopathy who promptly came to a normal level after a short period of proper feeding. There seemed to be no evidence of active tuberculosis, although this again was not rigorously excluded. The patient's asthenia was disproportionate in degree to that observed in pituitary or ovarian cases of a like degree of severity, as indicated by the objective measurements. On this basis a diagnosis of hypoadrenalism was offered tentatively and the experimental application of the Muirhead treatment recommended. The patient was referred from another city. We lost contact with the case and are ignorant of the outcome. While there are several evidences here which are more consistent with a functional adrenal deficiency than with that of another endocrinopathy, we regard this case as distinctly doubtful.

CASE B-323. The patient's chief complaint was of continuous backache, nearly constant headache, abdominal pain, and marked asthenia. In 1900, 25 years earlier, the patient received a severe blow on the coccyx, probably fracturing it. From this time she dates her backache. The coccyxgeal condition was not recognized for over a year, and then operation was regarded as unwise. Coincident with this trauma she developed an obstinate constipation. The menstrual function, which had been normal up to that time, became very irregular, with shortened interval, very profuse flow, and marked dysmenorrhea. After a long ineffective course of ovarian medication, surgery was invoked and a double salpingectomy, uterine suspension, and appendectomy were performed. Following this she became markedly asthenic, developed attacks of syncope, and the menstruation became very scanty; there was no improvement in her general condition. Still later a plaster jacket was applied to the spine and the backache was somewhat better during the period of its use. She was next given a vaccine treatment for arthritis, and finally a diagnosis of mucous colitis was offered. The backache has continued and is seriously inhibiting. She required special arrangements of pillows in her bed in order to lie with any degree of comfort. Latterly she has experienced formication in the lower extremities, also cramps, and deep muscle and bone pains. The onset of her headache was coincident with the initial trauma; it grows worse during the day and is increased by menstruation. It presents the anomaly that the headache subsides in some measure as the flow becomes more profuse. The abdominal pain was situated in the left lower quadrant and came on in the late afternoon. It was of short duration and at times so severe as to produce vertigo. The patient's fatigability has been progressive but is less marked in the morning. At times she is forced to lie down, and while she does not sleep and is conscious of people and of sounds, she is unable to rouse herself. A number of years previously she developed the morphine habit from the therapeutic use of the drug, but the condition was speedily corrected.

Family History disclosed no relevant details.

Past History: In addition to the episodes noted above, the patient recorded the usual children's dieases, abscessed ears and tonsillitis. She had had a tonsillectomy and a dilatation and curettage. She believed that the salpingectomy was performed because of a tuberculous condition of the tubes. The remaining history, including that of the menses, was not remarkable.

Physical Examination: The patient was a well developed and nourished woman of 40. The lips were somewhat cyanotic, the teeth widely spaced. The chest was apparently normal. There was a vague tenderness over the entire abdomen not really localized although possibly increased over the right kidney and in the right lower quadrant. There were brownish pigmented areas on the exposed surfaces, marked tenderness over the coccyx and sacro-iliac region, and a small cystic tumor at the level of the 12th dorsal vertebra over the spine which was not tender. Body hair was heavy but of normal distribution.

Laboratory Summary: The patient's vital capacity measurements were normal. The basal rate at a sub-normal level, with low blood pressure, slow pulse, and slightly sub-normal temperature. The CO_2 output was normal. The urine volume was normal; elimination poor; both albumin and casts were reported. Protein intake was somewhat low. The residual fraction of the urine was definitely above the normal. The 'phthalein test gave a borderline value. The blood chemistry was normal. Sugar tolerance was at half the predicted level. There was a distinct secondary anaemia, and the blood was leucoid in type.

Endermal Tests: The patient was not responsive to a large number of proteins.

Radiography: The coccyx showed a left lateral deviation. The skull was normal, as were the spine, sacrum and hips. The caecum was irregularly filled, the appearance raising a question of pylorospasm.

Orthopedic Examination: This confirmed the tenderness over the sacro-iliac region and determined a possible moderate relaxation of the joints. The small tumor growth was designated as a lipoma which was of no importance in the patient's case.

Pelvic Examination gave normal findings.

Eye Examination: Findings were normal.

Audiogram: Showed substantially normal hearing.

Neurological Examination: No organic nerve lesion was disclosed.

Discussion: The condition of the coccyx and lower back seemed to account for her backache. The defect in the function of the caecum could possibly have resulted from adhesions arising from her previous operation. It could also be due to a tuberculous condition, and the questionable pylorospasm could also be referable to either of these causes. From the endocrine standpoint, with a lowered basal rate and lowered sugar tolerance, a pituitary dysfunction, ovarian failure, and adrenal failure were all possibilities. The blood pressure was somewhat low for a pituitary failure; likewise, the blood uric acid was normal and there was no eosinophilia. The eye grounds were normal and there was yet other evidences which rendered a pituitary disorder improbable though not excluding it.

A primary ovarian failure can not be so readily excluded. It is true that the menstrual function showed irregularity and profusion, but the analysis of a long series of ovarian cases shows this particular formula to be the least common. The patient exhibited a definite anaemia, and this we have not observed to be the usual finding in ovarian failure although one to be expected when the adrenal is involved. The normal alveolar carbon dioxide, the leucoid blood, and distribution of body hair, are not characteristic of ovarian failure. As direct supporting evidence for the adrenal, the very low level of blood pressure, the marked fatigability, the evidences of renal impairment, may all be enumerated. The exposed surfaces were somewhat pigmented, and enquiry elicited the fact that none of her family showed a similar coloring. The normal blood sugar is by no means characteristic, but the patient was acutely sensitive to pain and nervously unstable, and this level might represent a slight response to the emotional stimulus which could be engendered in even hypofunctional adrenals. The patient had apparently had tuberculosis in the pelvis, and where tubes are thus involved there are usually other tuberculous areas. On the whole, while the case could not be regarded as clear cut, enough evidence presented to warrant a tentative diagnosis of functional hypoadrenalism. The Muirhead treatment was recommended and was followed for a short time after the patient returned home, with distinct evidence of improvement. It was subsequently discontinued and indirectly we have learned that the patient has relapsed into her earlier condition which is continuing adversely.

Here again is a case in which the main evidence to support the diagnosis is the response to treatment. We have already stated that we do not believe the therapeutic test convincing proof, but it seems worth while to record the findings, as only in this way will enough evidence be accumulated to clear up the very indefinite situation as regards "hypoadrenalism."

Clinically, there was certainly a large element of nervous and emotional instability in this patient, and the time honored diagnosis of neurasthenia can be rejected only because it fails to explain the objective findings. We believe that in this and many other instances the neurasthenia is the result, not the cause, of the metabolic disturbances, and that an attempt at their normalization is at least an essential part of the treatment of patients presenting, in addition to evidences of disturbed metabolism, signs of nervous instability. But we wish to make clear our belief that convincing demonstration of metabolic disturbance is an indispensable pre-requisite to such treatment.

CASE B-505. This is an incomplete case but the evidences are highly suggestive. The patient's chief complaints were of fatigue and fainting spells, tinnitus, and nausea. The patient had been married six years previously, having been well up to that time. Her baby was born five years ago. She failed to regain strength after confinement, and she dated her present condition from that event. She reported that she slept well but was always fatigued, the latter condition progressing during the day. The attacks of nausea developed two years previously and without any predisposing factor so far as the patient could tell. There was no vomiting; there was occasional pain under the left rib border, also low in the abdomen. The onset of the fainting spells was coincident with the nausea, and recently the patient had developed severe attacks of vertigo. The tinnitus was a recent manifestation. Two years ago she learned that her blood pressure was very low.

Family History: Two of three siblings died in early infancy.

Past History: The patient had one or two of the minor childhood diseases and scarlet fever. At the age of 5 she fractured her nose, producing a unilateral obstruction. A few weeks earlier there had been a severe blow to the head but radiograms of the skull showed no structural injury. She reported an occasional sensation of swelling in the upper eyelids, soft teeth, some chest pain, dyspnoea and palpitation. The bowels were regular but she was troubled with flatulency. The menstrual function had been entirely normal up to 2 years ago when for a period of one year she exhibited shortened intervals.

Physical Examination: The patient was a poorly developed and nourished woman of 26, ambulatory but seeming very weak. Obstruction of the right side of the nose and poor teeth were noted. The pulse rate was somewhat rapid. There was some enlargement of the proximal interphalangeal points; the skin was dark without heavy bronzing, and pilosity on the extremities was marked. The eyebrows were bridged, and there was a slight mustache, also some hair on the breasts. The abdominal hair was heavy but of normal distribution.

Laboratory Summary: The patient was a small woman 12 per cent below her predicted weight and definitely below her predicted lung volume. An unsatisfactory basal rate determination showed —11 per cent with very low blood pressure and somewhat rapid pulse. Repetition of this test was impossible as the patient began to menstruate, returned to her home in another state, and was subsequently felt to be too weak to return for a completion of the study. This episode influenced the completeness of the entire investigation. The alveolar CO_2 was normal. The urine volume was scanty, elimination fair only; both albumin and casts were reported. The protein intake was somewhat low, the residual nitrogen fraction high and the 'phthalein test definitely below the normal. The blood chemistry was fairly normal though the nitrogenous constituents showed an upward tendency in relation to protein intake. The blood sugar was below the normal level. The sugar tolerance was incomplete but was certainly 50 per cent below the normal, and from the amount of sugar excreted during the test probably at a still lower level. The blood showed a definite secondary anaemia without evidence of active degeneration; the leucocytic formula was substantially normal.

Nose and Throat Examination: The tonsils were apparently not offending. The nasal septum showed a sharp deflection to the right.

Pelvic Examination: Conditions were normal except for minor residua of child-bearing.

Eye Examination showed slightly enlarged blind spots; otherwise findings were normal.

Discussion: The whole general picture here is compatible with a condition of failure of the adrenals. The possibility of organic involvement was not excluded, but the incomplete character of the test robs a conclusion of any final authority. Muirhead treatment was recommended, but no further observation of the patient has been possible. Clinically the history is very suggestive of Addison's disease, including as it does the acute exacerbations of weakness and nausea found with proven adrenal disease.

CASE B-567. The patient's chief complaint was of a swelling of the legs and hips, with market distension of the scrotum. For the past 10 years the patient had had a chronic arthritis with involvement of the right shoulder and the hips. For the past two years there had been extreme pain at night along the course of the sciatic nerve. For a period of a few weeks before admission there had been much swelling of the feet, while the enlargement of the scrotum had appeared two weeks earlier.

Family History: One uncle died of tuberculosis; the history was otherwise not informative.

Past History: The patient had the minor ailments of childhood, a tonsillectomy at the age of six, and removal of cervical glands three years previously. Six months earlier he had developed iritis of the left eye and had been under continuous treatment for this condition. Some four months earlier he developed a diarrhoea and the use of an acidophilus culture intensified his condition. Under other medication there had been some improvement but he was still passing three or four loose movements daily. He gave a history of a blow on the testicle during boyhood that caused a swelling which subsided spontaneously after lasting for several weeks. He experienced some formication of the legs at such times as they were swollen.

Physical Examination: The patient was a poorly developed man of 25, requiring the use of a cane when walking. The skin was covered with acne, there was slight ptosis of the left upper eyelid, and the iris was cloudy; there was circumcorneal and conjunctival injection, also moderate photophobia with lacrimation. The right eye was normal. He exhibited herpes on the lower lip, the gums were pallid, and the teeth poor. The left chest was somewhat depressed, producing a definite asymmetry, and the left shoulder drooped downward and forward. The pulse rate was somewhat rapid, the blood pressure distinctly low. Beyond shallow respiration, the lungs were apparently normal. The scrotum was large and distended, and contained a large amount of fluid. The arms exhibited limitation of motion at the shoulder and at the right elbow, with some muscular atrophy. The knee joints were swollen and enlarged, tender, and limited in motion. From the knee down the legs were edematous. There was some bronzing of the skin on the lower extremities.

Laboratory Summary: The patient was slightly underweight and not significantly below his predicted lung volume. The basal rate as recorded was 16 per cent below prediction, with a normal pulse and very low blood pressure. Alveolar CO_2 was a low normal. The urine volume was scanty and the elimination poor. The urine contained albumin and sugar, while the sediment exhibited much epithelial debris and many granular and epithelial casts. His protein intake was inadequate; the residual nitrogen fraction was double the upper normal level. The 'phthalein output was low normal. The blood chemistry showed normal values entirely consistent with the level of the patient's protein metabolism. The blood sugar was low normal; the sugar tolerance, definitely depressed. The blood showed a slight secondary anaemia with an upward tendency to the leucocytes and a slight increase in the lymphocytes.

Examination for protozoa: Repeated examination at night failed to disclose the presence of filaria.

Electrocardiogram: The low voltage indicated an adynamic state consistent with adrenal disease.

Cardiac Examination: The heart was found to be normal. A very low blood pressure was recorded.

Orthopedic Examination: The patient presented generalized evidences of chronic arthritis in all stages of development. At the time of this examination the edema had affected the legs and the body as high as the second or third lumbar vertebra.

Eye Examination: The patient's left eye exhibited subacute inflammation, defined as kerato-iritis, with contracted pupil. The right eye was normal except for a slightly enlarged blind spot.

Radioscopy: Several abscessed teeth were demonstrated; both lungs were hazy, the left auricle prominent; the spine showed a general osteoporosis; there was destruction of the cartilage in both sacroiliac synchondroses; the right shoulder showed atrophic arthritis; both knees a hypertrophic condition, while the left hip showed both atrophic and hypertrophic processes. The gastro-intestinal appearances were normal.

Chest Examination showed conditions to be substantially normal.

Dental Examination: Several cavities and several infected teeth were demonstrated.

Genitourinary Examination disclosed no abnormality except the scrotal edema and that of the legs. The laboratory evidences did not show markedly impaired renal function.

Stool Examination: Ova and parasites were absent.

Discussion: A study of this case was felt to disclose the existence of two conditions which were by no means necessarily related. In the first place the patient had a definite arthritis of nearly ten years' standing, reported an earlier tonsillectomy, and exhibited a number of infected teeth. Second, there was evidence of nephrosis with edema, but without marked evidence of greatly lowered permeability. While asthenia was not stressed in the history, the patient was markedly fatigable and had been so for some time. The general laboratory picture accorded more nearly with that produced by adrenal failure than by any of the other endocrinopathies. A tentative diagnosis was offered of an early functional impairment of the adrenals. It is, however, recognized that the chronic focal infection, the arthritis, and the renal impairment, might account for most, if not all of the findings.

CASE B-940. This case is included because of the condition found at autopsy. The patient's chief complaint was of pain in the left side of the abdomen and the lumbar region. It had begun some three months earlier, had been progressively more severe and continuous, and was apparently unrelated to any event or habit of the patient's life. There had been a progressive loss of weight—some 40 pounds in the past three months—and a severe asthenia had developed.

Family History was entirely irrelevant.

Past History: The patient had had a few minor ailments in childhood, life-long weakness of the eyes following measles in this period, and one attack of influenza many years before. A tumor in the right breast had been successfully treated by electricity twenty years previously. She reported headache with nausea earlier in life; no attacks for many years. She was subject to rhinitis of a severe type. Though the patient was 68 years of age but few of her teeth had been removed. The appetite had been good until the development of the present illness. With its onset, however, she had developed nausea, flatulency, and diarrhoea. There was apparently an impairment in the sense of taste. Oliguria was a feature of the current complaint, previous to which, however, there had been nocturia. The patient matured early and the menstrual history was uneventful, including the menopause in the early fifties. In years past there had been a mild arthritis in the knees.

Physical Examination: The patient was a well developed woman of 68 showing evidences of much loss of weight. The pupillary reactions were very sluggish; the eyes showed incipient cataracts. There was some septum deviation and a moderate amount of crusting. The gums and teeth were in very poor condition. Smooth, firm masses were detectable over each clavicle, and there were several smaller masses in the neck. The heart gave a blowing systolic murmur, the pulse was slightly rapid. A large mass was felt in the left side of the abdomen, with possibly other masses in the epigastric and left inguinal regions. There were several tumor masses on the left thigh, the largest of which suggested a lipoma. There were a number of brownish pigmented areas on the upper body and lower extremities. The knee jerks could not be elicited, and there was a positive bilateral ankle clonus. A generalized adenopathy in cervical, axillary, and inguinal regions was recorded. The distribution of the body hair was entirely normal.

Laboratory Summary: The urine volume was very low and the elimination very poor. Albumin and sugar were both present, while the sediment showed many leucocytes, hyaline, and granular casts. The basal rate was +5 per cent with a somewhat low blood pressure and rapid pulse. The temperature was slightly sub-normal; alveolar carbon dioxide, normal. The patient was 2 per cent under her predicted weight but had lost nearly half her predicted lung volume. Protein intake was low, residual nitrogen high, and the 'phthalein output much below the normal. The nitrogenous blood constituents were distinctly above the normal level. The blood sugar was a high normal. The blood showed a moderate degree of secondary anaemia, and a definite leucocytosis with increase in the neutrophilic elements.

Laryngological Examination: The tonsils were enlarged and infected; the teeth in very poor condition.

Cardiogram: There was some evidence of cardiac impairment of a degree not inconsistent with the patient's age.

Radiography: Numerous infected teeth were demonstrated, and several retained roots. The skull was thickened but was otherwise normal. There was a large tumor mass on the left side of the abdomen reaching below the iliac crest; an additional large mass in the pelvis which showed numerous calcium deposits. The gastro-intestinal tract was normal except for redundant colon.

Eye Examination: The left eye showed an old choroiditis with scars producing an irregular partial central scotoma; the right eye was substantially normal.

Neurological Examination: This confirmed the evidences of a spinal cord lesion previously recorded.

Surgical Examination confirmed the presence of a tumor mass in the abdomen and the generalized adenopathy. The large tumor on the left thigh was diagnosed as a lipoma.

Orthopedic Examination demonstrated arthritis in the knees and spine, with possibility of malignant neoplasm in the latter.

Discussion: The case was diagnosed as general carcinomatosis, which was naturally inoperable. She was retained in the Hospital and died some four weeks after admission. At autopsy a large hypernephroma of the left kidney was disclosed with numerous metastases to the lung, liver, and the entire abdominal, peribronchial, thoracic, and cervical lymph glands. The right adrenal was normal. The left was so closely associated with the left kidney that microscopically it formed an integral part of the mass. This case is reported as that of a patient with presumptive destruction of one adrenal and exhibiting certain of the evidences which may be associated with adrenal disease. The normal basal rate constitutes a definite exception, while the patient's alveolar carbon dioxide is higher than that of any other case reported in this group. We have demonstrated in other cases of malignant neoplasm that the sugar tolerance is definitely lowered. The patient had malignant involvement of one kidney, while the other gave evidence of definite nephritic changes. From the differential standpoint the normal basal rate, in spite of the patient's grave condition, rapid loss of weight and lowered nutritional level, is significant. It might be inferred that the value obtained was an algebraic summation of the depleting factors already noted and an upward tendency engendered by the adrenal involvement. This is, however, purely speculative, and in the writers' opinion highly improbable.

From the clinical point of view, it is interesting to compare the findings in this patient with those cited above, and the fact that her symptoms are very similar to those of the other individuals in this group is important. Certainly there could have been impairment of adrenal function in this last patient, and if her symptoms are ascribable to that condition it may fairly be argued that the similar symptoms of the rest of the group might likewise be explained. It is, however, not safe to go so far, since this last patient had an abdominal tumor large enough to bring about mechanically her digestive symptoms, while her asthenia, and many of the laboratory findings may be fairly referred to the general carcinomatosis. So far as our series of cases is concerned it must be said that the case for hypoadrenalism is "suspected but not proved."

GROUP III. PUBERTAS PRAECOX

CASE C-16, et seq. The case of this little patient is reported because of its general interest and of a possible adrenal element. In our opinion this latter is far from established, although there are numerous references in the literature to an association of early puberty with certain types of adrenal disease. Many of these, however, lack objective supporting evidence, and this case is reported without prejudice and for consideration.

The child was admitted to the Hospital late in April, 1925, complaining of a gradual developing weakness of the arms and legs. As

TABLE XVII
"PUBERTAS PRAECOX"

Observation	Sex—Female								
Date	4 29 1925	7-28-1925	10-20-1925	1-26-1926	4 27-1926	6-29-1926	10 19-1926	6-25-1927	7-5 1928
Age (yrs.-mos.)	7-9	8-0	8-3	8-6	8-9	8-11	9-3	9-11	10-11
Height (cm.)	115	121	122.5	124	126.5	127.5	129	134.5	141.5
Weight (kgm.)	22.0	23.8	26.1	28.4	31.7	29.6	31.4	36.1	42.7
Weight Deviation (%)	—3	-5	—2	+4	+12	+2	+3	+9	+10
Lung Volume Deviation (%)	—	—51	—48	—38	—30	—34	—27	—28	—14
Basal Rate Deviation (%)	—29	—10	—18	—8	—24	—18	—24	—28	—21
Blood Pressure Sys	90	92	100	90	84	86	100	92	116
Dias	52	58	58	55	48	40	55	50	64
Pulse	94	102	100	92	90	84	84	77	86
Temperature	98.8	99.0	98.8	98.8	98.2	98.6	98.2	97.6	98.6
Alveolar CO₂	34	37	38	42	42	39	33	43	42
Urine Volume	480	850	550	620	570	330	740	560	640
Specific Gravity	1.007	1.010	1.018	1.014	1.019	1.016	1.012	1.024	1.018
Albumin	+	0	0	0	++	+	+	+	+
Casts	0	0	+	0	+	0	0	0	0
Sugar	0	0	0	0	0	0	0	0	0
Total Nitrogen	2.31	4.45	4.90	4.92	4.68	3.30	5.02	5.62	5.10
Residual Nitrogen	13.3	10.3	5.6	13.6	6.2	6.3	8.6	12.5	7.1
P. S. P. 2-hour	53	63	60	68	62	63	55	45	60
Galactose Normal	20	20	20	20	20	20	20 ?	30	40
Observed	20	20	10	10	10	10	30	30	40
Deviation	±0	±0	—50	—50	—50	—50	+50 ?	±0	±0
Blood Non-Protein N_2	34	31	33	—	28	33	26	27	32
Uric Acid	3.3	3.1	4.0	—	3.8	4.2	4.6	2.6	3.3
Sugar	112 ?	107	99	—	105	96	91	93	100
Haemoglobin	85	95	80	95	85	100	95	85	80
Erythrocytes	4.84	4.59	4.35	4.71	4.28	4.97	5.30	5.20	4.40
Color Index	0.88	1.03	0.90	1.01	0.99	1.01	0.90	0.82	0.90
Leucocytes	6.3	4.6	7.6	8.0	10.5	7.2	9.1	7.8	7.4
Neutrophiles	65	48	31	40	47	73	60	56	66
Lymphocytes	30	40	60	45	43	21	30	37	29
Eosinophiles	5	6	2	6	3	1	3	1	1
Endothelials	0	6	6	8	7	5	7	6	4
Misc	0	0	1	1	0	0	0	0	0

a matter of fact she was unable voluntarily to raise arm, leg, or even a finger. The condition dated back to May of the previous year when the child came home from school complaining of illness. After her arrival home she had a severe nose-bleed and vomited, but had so far recovered that she was able to return to school the next day although she complained of a severe headache. As the latter persisted she was kept at home and in bed for several days, during which the tongue became very yellow, and the child apparently temporarily lost the use of her legs. She again recovered from this in a few days, but shortly afterward was hit in the right leg, which caused her to limp for about three months. The right leg became progressively weak during this period and subsequently weakness developed in the left leg, in the hands, and in the arms. A tonsillectomy was followed by temporary improvement, but the child then developed pneumonia some three months before admission to our Clinic. During her attack of pneumonia she was seen by a number of physicians whose opinion was divided between a condition of progressive muscular atrophy and of infantile paralysis. At the time of admission here there was complete inability as noted above.

Family History was irrelevant.

Past History: Beyond the facts already noted the patient had had chicken-pox and measles, but otherwise up to the time of her illness she had been unusually well and strong. The catamenia had not been established.

Physical Examination: The patient was a well-developed and well-nourished child, seven years and nine months of age. She was unusually alert mentally, and distinctly mature. The physical findings in the main were normal. The child had no prehensile strength in her hands. The arms could not be flexed at the elbows, nor could the legs and thighs. There was neither adduction, abduction, or flexion in legs and hips; the right leg was somewhat atrophied, and there was foot drop in both extremities. The knee jerks and wrist jerks could not be elicited; there was no ankle clonus. The Babinski and Oppenheim reactions produced flexion. There was abundant hair growth on the legs, arms and external genitalia. The skin was white and free from pigmented areas.

Laboratory Summary: The child was within 3 per cent of her predicted weight. The lung volume could not be ascertained. The basal rate deviation was 29 per cent below prediction. Too much weight should not be given to the absolute magnitude of this datum, as standards for female children of this age are far from well established. The relative value, however, is significant when compared with the later measurements. The pulse was distinctly rapid, the blood pressure somewhat low. The urine volume was somewhat scanty, the elimination poor, and albumin was present. The total nitrogen showed an entirely inadequate level of protein metabolism. The residual nitrogen fraction showed an upward tendency. It is to be borne in mind that with lowered protein intake in the normal individual, the relative value of this fraction tends to increase. On the other hand, the patient was a seven-year-old child weighing but 22 kilograms, hence her protein level was not as low relatively as would be connoted by the same nitrogen elimination in an adult. The 'phthalein output was low normal. The sugar tolerance was normal. The blood nitrogen values were relatively high but within the conventional normal limits. The blood sugar was slightly high but this could have been due to an emotional response. The blood morphology showed somewhat low values throughout, the sole exception being a 5 per cent eosinophilia.

Radiography: The spine, pelvis and sella were normal; the skull somewhat rachitic in shape. The mediastinal shadow was 5.5 cm. in diameter. The heart and lungs were normal.

Neurological Examination: A fine muscular palsy affecting the lower extremities, pelvic girdle, and the shoulder girdle was observed. In the examiner's opinion the atrophy was absent which would be expected in a case of anterior-poliomyelitis. Final opinion was reserved.

Discussion: While the child had not established the catamenia, she had a marked growth of pubic hair and the body configuration suggested a beginning maturity. While, as noted above, too great weight could not be placed on the absolute value of the basal rate, it was evident that there was a marked lowering from the level to be predicted in health. The child was under proteinized, which could be a factor, but was not undernourished. There was evidence of a lowered kidney permeability. The child was definitely asthenic; on the other hand, the sugar tolerance was normal. It was felt that the illness which the child had experienced had not been properly evaluated. It was impossible to get additional details, but there seemed to be no question that the present condition had followed the somewhat vague attack described above. Many of the features were consistent with adrenal impairment, although a thyroid failure could not be excluded with certainty in view of the low basal rate and the normal sugar tolerance. The complementary features of a thyroid failure were, however, entirely lacking. On this basis a tentative diagnosis of adrenal dysfunction was offered and treatment by adrenal cortex suggested. Through the coöperation of the parents, the child was returned to the hospital some three months after our first contact. In the meantime she had been receiving adrenal cortex. It was found that there was a definite improvement in many ways. The whole general musculature had become much stronger, the child was able to raise hands, arms and legs when in a recumbent position. Some atrophy in the extensors of the hands with slight contractions on flexion; foot drop, and marked weakness in the extension of the toes were still apparent. A thorough neurological examination and review of the case, for which we are indebted to Dr. N. H. Garrick, ruled out anterior poliomyelitis and progressive muscular atrophy. In his opinion the vague illness which was the starting point of the whole condition could possibly have been an unrecognized diphtheria, and the muscular condition which was its sequel, a postdiphtheretic paralysis. From the laboratory standpoint the basal rate was found to have increased to the low normal borderline. The patient had grown 6 cm. and increased in weight 1.8 kgm. The pulse was slightly higher, the blood pressure practically unchanged; the alveolar carbon dioxide had increased to a low normal level; the urine volume had improved, as had the elimination; the protein intake was double, which naturally could have some influence on the improvement in the basal rate. The residual nitrogen fraction was lower, though still high, and the 'phthalein output had increased to a satisfactory normal level. The sugar tolerance remained unchanged. The blood chemistry had improved somewhat in spite of the increased protein intake. The blood morphology showed a slightly lower red count, a slight leukopenia, an increase in the lymphocytes, and a persistence of the eosinophilia. Adrenal cortex medication was continued, and three months later the child was tested again. The weight had improved, the basal rate had subsided to a point midway between the earlier records, sugar had appeared in the urine, the residual nitrogen had become normal, the sugar tolerance had dropped to a level below the normal, a slight secondary anaemia had developed, the lymphocytes had risen to 60 per cent of the normal leucocyte content, while the eosinophilia had disappeared. It is unnecessary to review all of the data of the repeated tests performed on this child in the table given above. Suffice to say that she has regained full use of her arms and hands, there is still a residual toe drop which is being gradually overcome under orthopedic correction. She can walk and run with considerable freedom. The sugar tolerance, while remaining at a depressed level for a period, in September, 1926, exhibited a marked increase to a point above the normal, which was interpreted as indicating an approaching onset of menstruation; this latter was established a few months later, when the child's tolerance became normal and has remained so up to the present time. Adrenal cortex was discontinued after the first marked improvement, and the child has progressed satisfactorily without recent therapeutic aid. The basal rate has remained low, the blood pressure has steadily improved to a present normal level, and the somewhat rapid pulse has given evidences of subsidence. The alveolar carbon dioxide has become entirely normal. The general normalizing of the other factors is apparent from the table. In view of the child's marked improvement it has been felt best to avoid further endocrine medication. She reports yearly to the hospital and a thorough study is carried out. In time it seems probable that it may be wise to resume endocrine therapy. The need for it at the present time, however, has certainly not been demonstrated.

As was stated in the beginning, we have no desire to be dogmatic about this case. It may be permitted, however, to indulge in some speculation, recognizing that it is no more than this. If we assume the accuracy of Dr. Garrick's diagnosis of an earlier diphtheria producing a post-diphtheretic paralysis, we have a patent explanation both for the initial muscular weakness, and equally for its gradual improvement with the passage of time. This, however, would fail to explain the child's early evidences of maturity, and might not entirely account for the very rapid improvement of the muscular condition during the initial phase of her therapy. If the adrenal be a detoxicating organ—and there are many who believe it so to be—it is conceivable that it had passed through a phase of over-stimulation as an incident to the toxaemia arising from the patient's diphtheria. Evidence would seem to indicate that with certain of the endocrine glands such a period of overactivity is followed by a compensatory lowering of functional level. That precocious puberty arises in an overactivity of the gland, is in no small measure assumptive. The presence of a tumor of the cortex does not necessarily connote a functional overactivity, but may imply the reverse. Be that as it may, it is possible that the early maturity of this little patient had its origin in impulses from changed adrenal function which in turn derived from the earlier toxaemia. It is interesting to note that the child's persistent thymus exercised no deterring effect on the progress of her maturation. The case is offered merely for consideration. Continuance of the study may, at some future date, throw light on the underlying etiology. That a thyroid element, as suggested by the present basal rate and sugar tolerance, could enter in, is entirely contrary to the very large number of existing records where thyroid failure at this age has produced a complete opposite effect. That vague and dubious entity, a hyperovarianism, cannot be invoked, as at no time had the child shown an increased galactose tolerance with the exception of one observation shortly before the onset of menstruation, and here the fault unquestionably lies with the definition of the standard, and the patient's tolerance was consistent with the physiological stadium. A pituitary factor could find some support, as the child has shown irregularly an eosinophilia, a high blood uric acid, lowered basal rate, and a lowered sugar tolerance. In a long series of pituitary cases, however, we have never studied a patient who showed so marked a depression of the basal rate while exhibiting a normal sugar tolerance. Pituitary cases, transitional between an initial hyper and terminal hypo-activity of the posterior lobe, may be studied fortuitously while the sugar tolerance is passing through the normal zone. We have observed a few such cases, checking the accuracy of the initial inference by subsequent study of the case after the transition has been completed. While the anterior lobe seemingly undergoes involutional activity to a hypofunctional level more readily and rapidly than the posterior lobe, we have never observed a case in which the anterior lobe has been so far ahead of the posterior in its transitional adjustments. Finally, a stimulating influence on the genital sphere is observed in overactivity, not failure, of the pituitary. The case for the pituitary then would seem to lack substantial support, and we feel constrained to conclude that if the patient be endocrinopathic the adrenal would seem to be the most probable focus of involvement.

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Reprinted from ENDOCRINOLOGY, The Bulletin of the Association for the Study of Internal Secretions, 1214 Wilshire Medical Bldg., Los Angeles, California, Vol. 13, No. 1, January-February, 1929, Pages 1 to 39.

STUDIES OF THE ENDOCRINE GLANDS
VI. PLURIGLANDULAR SYNDROMES

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In a series of previous communications the details of an objective method for the differential diagnosis of endocrine disorders have been reported (1) and the results collected which have been obtained by its application to certain members of the ductless glandular group.*

The present paper deals with a small group of cases (22) in which morbidity of more than one endocrine focus was capable of demonstration—in other words, the so-called pluriglandular syndromes. Readers of the earlier papers of this series will have surmised that the authors do not subscribe to the current orthodox idea of the frequency and significance of the conditions thus designated. The present meager group represents the careful selection from a series of nearly four thousand patients examined, and are the only ones seemingly in which multiglandular involvement could be certainly demonstrated. This does not imply that in a large number of endocrine cases evidence of impaired function will not be found in endocrine centers other than that in which the basic condition finds its origin. But these manifestations are purely secondary and as much the result of the general metabolic disturbance as are the concomitant malfunctions of a large group of non-endocrine entities. Further, there can be but little question that primary functional disturbance of rigorously non-endocrine tissues will engender perverted activities of the endocrine group as components of the complete human mechanism. The authors' position may be summarized as a sincere desire to separate cause from effect and to avoid the endowment of sequelae with the authority of a primary causative significance. To illustrate with but one example from the many, it is a frequently recorded fact that serious malfunctions of either the pituitary or the thyroid engender, among many other symptoms, an impairment of the menstrual function. This may become a true amenorrhœa in cases of established gravity. Though the menstrual function presumably has its origin in certain of the cells composing the ovary, and is an external manifestation of an exocrine activity, the popular opinion that regards the control of this function as implicit in the internal secretory activities rests, after all, upon certain assumptions which are not entirely based upon controlled objective facts to support it. Amenorrhoea may exist with seemingly normal ovarian endocrine activity, and patients with severe gonad failure may exhibit normal menstrual function. Castration and transplantation experiments are not germane to the thesis, as all portions of the gland inevitably participate.

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*Rowe and Lawrence (Pituitary) (2); Lawrence and Rowe (Thyroid) (3); Rowe and Lawrence (Gonad) (4).

The assumption, then, that a pituitary or thyroid amenorrhoea implies a primary participation of the internal secretory activity of the ovary is the result of an elaborate synthesis of unsupported speculations which have, however, been so frequently repeated as to assume with many the authority of established fact. Sight is lost of the fact that with no valid evidence of an interdependence between endo- and exo-crine functions, one rather sweeping assumption becomes vital to the thesis. In this connection, as stated above, we have frequently observed amenorrhœa with no objective evidence of other than normal ovarian function, and equally, many subjects have been studied demonstrating a definite gonad failure and reporting an entirely normal menstrual history. Only in those anatomical and structural changes in which all portions of the gland participate, do we necessarily find simultaneous inhibition of both internal and external activities. To go but one step further, the existence of amenorrheas of a rigorously non-endocrine origin is generally recognized, as those, let us say, of cardiac or renal origin. If the multiglandular theory be adopted, it becomes necessary to infer a primary gonad failure in these conditions, a conclusion which is not only devoid of any supporting evidence, but against which an impressive array of observed and tested facts can be marshalled. This constitutes a second vital flaw in the chain of speculative reasoning. Without dwelling further on this phase of the topic, it may be said that objective fact imposes straiter limits than does subjective theory.

The advocates of pluriglandular doctrine range from those who see in every phase of endocrine malfunction an algebraic summation of disturbed activity of all the members, established and putative, of the family of ductless glands,* while others, with a larger measure of conservatism, restrict the concept to those more or less well defined disease pictures which are frequently designated by the names of their proponents.† These represent extremes of thought, and between them is found a protean array of intermediate theories. That the polypharmacy of the manufacturing drug houses has played an important role in confirming an uncritical acceptance of the general concept, must be recognized.§ The scientific warrant for the administration of a complex mixture of glandular extracts is certainly tenuous, and the exhibition of a combination containing ovarian and mammary substance to the male sufferer conjures up pleasing vistas of speculation.*

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*In the first group (among others, Keith [5], and Berman [6], should be numbered those writers who courageously discount all cosmic influences and regard ethnic types as determined physically and psychically by intriguing permutations of function in which the whole endocrine family participates. It is unfortunate for the general acceptation of these broad and stimulating generalizations that no objective evidence has as yet been adduced that offers the faintest support.

†In this category fall the "multiple ductless glandular sclerosis" of Falta (7), Timme's (8) "thymus-adrenal-pituitary" compensatory syndrome, and the numerous complexes suggested by the clinical workers of France.

§The reductio ad absurdum has recently appeared in a widely circulated device with which by means of a slotted rotating disk any given symptom can be mechanically correlated with the correct pluriglandular preparation designated by number. As a basis for diagnosis and treatment this compares well with a crystal ball or the intricate arrangement of tea leaves.

To avoid misunderstanding, a statement in the earlier part of this paper must be reiterated. Many of the existing contradictions and disagreements concerning multiglandular disease rest on the artefactual basis of a question of terminology. The endocrine glands, those at least whose warrant to this designation has been clearly indicated, are among the important regulators of general body metabolism. In the enormously intricate interlocking directorate of the animal mechanism there exist an unguessable number of balanced and delicately adjusted equilibria. The existence of protective compensatory mechanisms forms a necessary corollary to the initial concept and these provide for readjustments to meet the constantly changing conditions inherent in the life processes. With a serious derangement, from whatever cause, such compensations are perhaps not effective, or at the best, only partially so. A pertinent and relatively simple illustration of this point is offered by the regulation of the hydrogen ion concentration of the blood shown in health and disease. Intricate though it be, present knowledge would indicate for it a far greater simplicity than for many other necessary functions which physiology is defining and interpreting. When a disturbed condition arises, many of the functional equilibria are influenced, not in equal measure but in varying degrees. Such changes of level engender others, and in these ramifications of an initial impulse, a vast number of end results will appear in the form of more or less profoundly altered functional levels. Frequently, as we see in any well characterized syndrome, a certain group of common manifestations will be engendered, differing among themselves in degree but not in kind. Contextually, a horde of minor divergences become manifest, portraying the influence of individual difference. As a corollary to this we should equally expect one certain end result, of well defined character, to arise from a wide diversity of causes. The same illustrative mechanism already noted will serve to exemplify this point. Acidosis, an end result, is the increase of the hydrogen ion concentration of the blood. The many divergent origins producing this single final product are too well known to require statement. Any given symptom may be a result of any one of a number of wholly dissociated initial causes, and this fact should never be ignored in establishing relationship between effect and cause. Causal elements must be individually evaluated and the final allocation be determined by exclusion.* With the endocrine glands integral and in some cases essential factors in the body complex, it is obvious that disturbed function in one of them, from whatever cause, will engender resultant disturbances in other members of the group. Equally, however, in the breaking down of normal relationship, a whole series of other foci of control will be subversively affected and their functional levels likewise exhibit change. In this sense, we have pluriglandular disease, but to preserve a just parity, we must apply the same term to those conditions of non-endocrine origin in which the ductless glands participate as secondary and resultant stadia in the progress of the condition. The adoption of such a just and equitable classification would hardly prove constructive in the diagnosis and treatment of disease. Differentiation is the prime requisite, and the larger the measure of specialized function, the greater the opportunity for eliminating, or more usually, partly inhibiting superimposed extraneous influences. Man, rather than the amoeba, is the subject of election for functional study.

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*Happily many of these preparations are practically inert and their administration allows of all possible psychic benefit without physical injury. Occasionally cases present, however, where this negative benefit does not obtain, and acute conditions have arisen from injudicious use. The greatest single need in the field of glandular therapy today, is the single substance whose physiological activity has been standardized by some dependable biological method of assay. Some progress has been made but much remains to be done. The determination of the iodine content of a thyroid preparation as an index of activity is on a parity with the standardization of digitalis by an estimation of the glucose content. Further discussion is unnecessary here since a paper treating this whole question is shortly to appear.

Recognizing a mutual interdependence of the ductless glands—in common with all other parts of the mechanism—it is only to that assumption of special esoteric interrelationship as implicit in this single group to which the authors take exception. And the ground upon which this opinion rests is the careful study, by purely objective methods, of individuals in whom a presenting disorder was the result of demonstration and not of inference. If, for example, as a uniform and unvarying result of the removal of the ovaries in adult womanhood and before the menopause, it is observed that the power of assimilation for galactose is reduced by 50 per cent, one is warranted in assuming that some relationship seemingly exists between carbohydrate metabolism and an influence exercised by the presence or absence of these glands. Such a fact has diagnostic significance when supported by an adequate number of other tested facts. Finally, the authors wish to emphasize that at no time do they deny the possible existence of a true pluriglandular involvement. With the numberless permutations and combinations possible, it would indeed be remarkable if cases did not exist in which a simultaneous primary malfunction was exhibited. In the present series there are a few cases in which such a condition seems to obtain. With such cases, however, as infrequent as they have been found to be, we tentatively suggest that their pluriglandular designation may derive from our own imperfect knowledge rather than from a true multiple involvement. In any case, in our experience, true pluriglandular syndromes, if they exist, are seemingly of the greatest rarity.

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*The present method of differential diagnosis is based on the principle, with the added factor that the endocrine element comes to consideration only after possibly causal non-endocrine disease has been eliminated by test and observation.

It is not necessary to protract this discussion further. Additional supporting evidence for the general thesis constitutes a part of the papers which have already appeared. Further, there is every reason to believe that among many workers in this field the term "pluriglandular" is used in the same restricted sense that here obtains.

Turning to the component members of this series, a necessary preliminary statement is the designation of the individual case with indication of the glands involved. These facts are presented in Table I. (See next page).

Of the 22 cases here listed, 17 owe their plurality to the coexistence of a functional error in one gland with the result of surgical alteration of another endocrine focus. Of these, 14 are complete castrates, while 4 were postoperative cases after thyroidectomy. The seeming arithmetical contradiction, as inspection of the table will show, depends upon one case with surgical intervention in more than one gland. In the light of the previous discussion, the five remaining cases offer a peculiar point of interest. As they will be discussed in detail in the body of the paper, it may be briefly stated that cases B-532 and B-37 are the only ones in which some modifying circumstance does not present. B-18, seen in early middle life as a thyroid failure, had had a pituitary hyperfunction in prepubertal years with some evidence of a residual posterior lobe overactivity. Her inclusion in the group is partly conventional. S-568 is a frankly doubtful case, the thyroid dysfunction determining her presenting symptoms and the pituitary element resting primarily on the very dubious ground of a seemingly distorted sella. S-686 was a partial castrate and falls between the disease and surgical groups.

TABLE I

Glands Involved with Character and Origin of Derangement

Group	Case Number	Function	Pituitary			Thyroid		Ovary	
			Ant.*	Post.	Origin	Func.	Origin	Func.	Origin
I—a	B-37	dys.	—	—	Dis.	—	Dis.		
b	B- 18	dys.	—	+	Dis.	—	Dis.		
	B- 532	dys.	—	+	Dis.	—	Dis.		
c	B- 141	dys.	N or —	+	Dis.	±	Surg.		
	S- 568	dys.	N or —	+	Dis.	±	Dis.		
II—a	B- 659	hypo	—	—	Dis.			—	Surg.
	S- 744	hypo	—	—	Dis.			—	Surg.
	S-1327	hypo	—	—	Dis.			—	Surg.
	S-1343	hypo	—	—	Dis.			—	Surg.
	S-1669	hypo	—	—	Dis.			—	Surg.
III—a	S- 686	hypo				—	Dis.	—	Dis.
	B- 109	hypo				—	Dis.	—	Surg.
	B- 599	hypo				—	Dis.	—	Surg.
	B- 662	hypo				—	Dis.	—	Surg.
	B- 976	hypo				—	Dis.	—	Surg.
	S-1843	hypo				—	Dis.	—	Surg.
b	S- 179	dys.				±	Surg.	—	Dis.
	S- 230	dys.				±	Surg.	—	Surg.
	S- 988	dys.				±	Dis.	—	Surg.
	S-1023	dys.				±	Dis.	—	Surg.
	S-1069	dys.				±	Dis.	—	Surg.
IV—a	B- 164	dys.	?	+	Dis.	±	Surg.	?—	Surg. Dis.

*The indicated functional levels of the anterior lobe are tentative and based on probability.

The presentation of our data in tabular form, never entirely satisfactory, is peculiarly hampered in the present instance. With the permutational possibilities on the one hand, and the frequently contrary effects of the several malfunctions on the other, the salient differences shown by the individual cases merge when summated in an average. Some of the cases fortunately present sufficient similarity to make averages typical. In the Pituitary-Thyroid group this helpful condition is lacking. As the individual protocols form a part of this paper, in the interest of economy of space and a just recognition of the intrinsic limitations, we have merged these cases into three sub-groups which are not wholly dissimilar.

In the following discussions, cases will be designated as "hypofunctional" (—) in which all of the observations indicate lowered activities of the glands involved, while "hyperfunction" (+) indicates the antithetical condition. "Dysfunctional" (±) cases are those where evidence of both phases of activity are seemingly present in a single gland, or where the two glands are at different functional levels. The authors adopt this convention—which is not devoid of sanction—to avoid unproductive and space-consuming dialectic. The definition, at least, permits the reader to visualize the symptom complex.

In the subsequent tabulations, Case B-976 in Group III-a will be omitted. This patient is the only male in the entire series, and his inclusion would only add one more disturbing element to the difficulties of collective presentation.

TABLE II

Physical Measurements

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Number of Cases	2	2	2	5	5	5	1
Age, Av. (yrs.)	51	36	53	49	42	44	40
Height, Av. (cm.)	166	177	171	158	165	160	147
Sitting Height, Av. (cm.)	86	92.5	89.5	86	88	87	81.5
Sitting Height, Index	0.518	0.523	0.523	0.544	0.533	0.544	0.554
Chest, Av. (cm.)	107	89	87	81	76	79.5	80
Weight, Av. (kgm.)	106.2	84.4	70.6	63.1	61.9	67.6	59.8
Area, Av. (sq. m.)	2.13	2.00	1.87	1.64	1.68	1.70	1.52
Lung Volume, Av. (cc.)	1720	3620	2600	2260	2720	2440	2000

Table II contains certain statistics and, incidentally, as measurements are absolute, realizes the worst possibilities of this method of presentation. The dominance of castration as a source of plurality determines the large incidence of cases with gonad involvement. The average ages are higher—well over forty as opposed to the low thirties of the other groups already described. The greatly lessened incidence of surgical intervention with the endocrine glands in childhood, is probably the determining factor. The average heights are not remarkable, the six feet three inches of B-18 being partly merged in a less conspicuous total. The pituitary cases would seem to have a slight upward tendency, however. Sitting height indices show some variation, the more significant as the whole series is confined to one sex. The single case in Group IV gives a value suggestive of achondroplasia, and those in II-a and III-b are definitely above the normal. Pituitary, reinforced by thyroid, determines an obesity suggested only in one sub-group of the Thyroid-Gonad combination. The lung capacities give evidence only of a general influence, and the other data reflect the height and weight relations. As is to be expected, every effort to formulate relative influences in mathematical terms has been

TABLE III

"VITAL CAPACITY" MEASUREMENTS

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Weight—							
High (%)		+24	+14	+52	+31	+36	
Low (%)		— 3	+12	— 5	— 4	— 5	
+ Average (%)		+24	+13	+21	+31	+14	
Percent of Group		50	100	60	20	80	
— Average (%)		— 3	—	— 3	— 9	— 5	
Percent of Group		50	0	40	80	20	
Net Average (%)	**+78**	**+11**	**+13**	**+12**	**— 1**	**+10**	**+22**
Chest—							
High (%)		+23	+16	+22	+20	+30	
Low (%)		∓ 0	+ 7	+ 5	—18	— 4	
+ Average (%)		+12	+12	+ 8	+12	+12	
Percent of Group		100	100	100	40	60	
— Average (%)		—	—	—	—12	— 4	
Percent of Group		0	0	0	60	40	
Net Average (%)	**+43**	**+12**	**+12**	**+ 8**	**— 3**	**+ 6**	**+12**
Lung Volume—							
High (%)		+ 3	—24	—16	— 2	—14	
Low (%)		— 9	—28	—39	—36	—40	
+ Average (%)		+ 3	—	—	—	—	
Percent of Group		50	0	0	0	0	
— Average (%)		— 9	—26	—28	—18	—24	
Percent of Group		50	100	100	100	100	
Net Average (%)	**—48**	**— 3**	**—26**	**—28**	**—18**	**—24**	**—29**

unproductive. Possibly with large groups (fifty or more) presenting closely related functional levels in each combination, statistical analysis might yield a first approximation. Only a later generation will have adequate data. The application of the method of least squares to a few cases is not even a diverting mathematical pastime.

With properly established standards, comparative values enjoy a significance of which the absolute raw data are devoid. Such a comparison, under conditions already described (1), are found in Table III.

The Pituitary obesities are here more strikingly indicated, although curiously enough three castrates with bilobar failure exhibit weights closely in accord with prediction. The small number of cases prevents the observation from being more than interesting. The chest comparisons logically repeat those on weight. All of the groups except I-b show a lowered lung capacity. The pluriglandular group is the lowest of our several series. Seemingly the double burden plays a part.

TABLE IV

Urine Measurements

Group.................	I			II	III		IV
	a	b	c	a	a	b	a
Glands................	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function..............	— —	± —	± ±	— —	— —	± —	±
Volume.........Av. (cc.)	2650	1300	1430	1470	1410	1130	1600
Specific Gravity......Av.	1.008	1.018	1.022	1.014	1.013	1.017	1.014
Albumin............(%)	100	100	0	40	40	60	100
Casts..............(%)	0	50	0	0	0	0	100
Sugar..............(%)	0	0	100	0	0	20	0
Salol.........Av. (min.)	165	85	60	—	85	—	60
P. S. P. Elim...Av. (%)	60	54	56	53	51	59	50

The urine data of Table IV offer a few points of interest.

A depressing effect on urine volume of thyroid and ovary is possibly reflected in the total group averages which are, I—1620 cc., II—1470 cc., and III—1270 cc. Less certainly can be traced a thyroid influence on the appearance of albuminuria, the relative percentages being, I—60, III—50, and II—40. A posterior lobe failure apparently compensates for the glycosuric effect of castration in Group II no more than does the hypoactive thyroid in Group III-a. The indications of the phthalein test are not remarkable.

The Nitrogen Partition values (Table V) might be interpreted as indicating an increased influence of the Gonad over Pituitary and Thyroid in the production of a high Residual fraction. Comparison with the data from the series of unglandular involvements in the preceding papers shows this not to be the case, however. The values here signify no more than that the metabolic error reflected in a high residual nitrogen is shown by all of the endocrines—and other studies betray a similar result in a fairly large group of non-endocrine diseases.

TABLE V

NITROGEN PARTITION

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Total Nitrogen, Av. (gms.)	**12.17**	**9.20**	**9.84**	**9.17**	**7.03**	**10.02**	**9.71**
Urea Nitrogen... Av. (%)	**81.1**	**80.5**	**76.7**	**78.6**	**80.4**	**80.6**	**89.7**
Uric Acid Nitrogen Av. (%)	**2.4**	**2.5**	**4.6**	**2.1**	**2.1**	**2.1**	**1.5**
Ammonia Nitrogen Av. (%)	**4.6**	**6.2**	**2.0**	**4.3**	**4.8**	**4.2**	**3.6**
Creatinin Nitrogen Av. (%)	**4.4**	**5.4**	**4.5**	**4.6**	**4.8**	**3.8**	**3.1**
Residual Nitrogen Av. (%)	**7.5**	**5.4**	**12.2**	**10.4**	**7.9**	**9.3**	**2.1**
% = or above 9%......	**0**	**0**	**100**	**60**	**20**	**60**	**0**

The chemistry of the blood, as presented in averages (Table VI), offers but little information. The relative uric acid increase, which is characteristic of uncomplicated pituitary malfunctions, is here not strikingly present (30 per cent in pituitary as against 20 per cent in non-pituitary cases). We record the fact without offering explanation. Residual nitrogen values assume significant heights only in the single case of Group IV. That this latter should exhibit it is not surprising in the light of her chronic interstitial nephritis and diverse endocrine pathology. The blood sugar sequence is not remarkable, the lower value in the Hypo-Thyroid-Gonad group being probably fortuitous.

TABLE VI

Blood Chemistry

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Non-Protein Nitrogen Av. (mgm.)	38	30	31	32	33	34	44
Urea Nitrogen Av. (mgm.)	19	16	16	15	16	17	21
Uric Acid Av. (mgm.)	5.0	3.2	3.4	3.6	3.6	4.0	6.0
Net* % = or above 4 mgm.	0	50	0	20	20	20	0
Creatinin Av. (mgm.)	1.9	1.4	1.4	1.5	1.5	1.5	1.4
Residual Nitrogen Av. (mgm.)	16.7	12.3	13.3	15.2	15.2	15.1	20.5
Sugar (mgm.)	127#	97	99	98	87	103	97

*All cases demonstrating nephritis have been deleted.
#Value too high. Patient was very obese and blood obtained with difficulty.

In the Blood Morphology (Table VII), two or three apparent relationships present. The tendency toward a secondary anaemia of Groups II and III, and the higher level of the lymphocytosis in Group III, are probably apparent rather than real. The association of an eosinophilia with the pituitary cases harmonizes with the observations with the uncomplicated cases. No record of serological findings is tabulated, as the response to the several tests was uniformly negative.

With the data of the Respiratory Metabolism (Table VIII), we find almost for the first time clear evidences of the summation effects of the several glands. This is probably due to the fact that again we are dealing with relative values, and the several magnitudes assume a concrete significance through the use of a standard of comparison allowing for individual variation. With the thyroid recognized as the primary regulator of the basal rate—at least in the group under consideration—with the pituitary and gonad on a basis of approximate parity—the pituitary perhaps slightly more effective—we should expect to find real differences. Pituitary and Thyroid failure together determine the lowest level, and while the dominance of the Thyroid is again manifest in the Thyroid-Gonad failures, Pituitary and Gonad together cannot lower rates to the depth which participation of the Thyroid connotes. Equally, antagonistic levels are strikingly shown in the several dysfunctional groups. The single case in Group IV probably shows a residual hyperactivity of the thyroid which compensates the depressing effect of the conjoint gonad and anterior lobe failures. Blood Pressures and Pulse Rates show similar tendencies but without the clarity of definition of the Basal Rate measurements. As noted in the table, a single hypertensive case in any one of these very brief series influences the group average unduly. The effect of the Gonads on Alveolar Carbon Dioxide is not strikingly exhibited in the presence of either the Pituitary or of the Thyroid.

TABLE VII

BLOOD MORPHOLOGY

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— –	± —	±
Haemoglobin....Av. (%)	**100**	**90**	**88**	**86**	**89**	**83**	**100**
Color Index	0.76	0.94	0.84	0.88		0.90	0.90
Erythrocytes....Av. (10^6)	**6.56**	**4.80**	**5.22**	**4.87**	**4.77**	**4.59**	**5.56**
Leucocytes.....Av. (10^3)	**10.0**	**7.4**	**5.6**	**8.9**	**8.2**	**8.2**	**7.9**
P. M. N. Neutrophiles Av. (%)	**60**	**56**	**54**	**57**	**55**	**46**	**57**
% =or above 75%	0	0	0	20	0	0	0
Lymphocytes....Av. (%)	**34**	**35**	**39**	**35**	**36**	**49**	**37**
% =or above 33%	100	50	100	60	60	100	100
Eosinophiles.....Av. (%)	**1**	**3**	**2**	**4**	**2**	**1**	**1**
Net* % =or above 3%	0	50	50	40	20	0	0
Monocytes......Av. (%)	**5**	**6**	**5**	**4**	**7**	**4**	**5**

*All cases demonstrating a non-endocrine cause of eosinophilia have been deleted.

As with the Respiratory Metabolism, the additive character of the carbohydrate influences gives a true significance to certain of the collective averages. For the sake of clarity, the reader may be reminded that the level of tolerance for galactose for the normal adult female is at forty grams. Castration or severe functional failure of the gonads lower this to twenty grams, less severe to thirty, the stadia being determined by the conditions of applying the test and not implying abrupt transitions. The posterior lobe of the pituitary may condition, by overactivity, a complete extinction of the tolerance, or equally, by a lowered function may raise it 200 per cent or more. With the thyroid, the sense of the change follows the pituitary, but the magnitude varies widely and significantly. Over two-thirds of the thyroid cases show a normal tolerance (for galactose), and the remainder exhibit changes of the order of ±33 per cent. Finally, in the normal sex cycle immaturity connotes the same level as that of castration, while the menopause may produce no change or more usually a depression to thirty grams. The data derived from the application of this test are given in some detail in Table IX.

TABLE VIII

Respiratory Metabolism

Group	I			II	III		IV
	a	b	c	a	a	b	a
Glands	Pituitary Thyroid			Pituitary Gonad	Thyroid Gonad		Pituitary Thyroid, Gonad
Function	— —	± —	± ±	— —	— —	± —	±
Basal Metabolism							
Deviation—High...(%:		—22	— 3	— 7#	—21	— 6	
Low....(%)		—44	—25	—23	—30	—14	
Average..........(%)	**—34**	**—33**	**—14**	—20	**—26**	**—11**	**— 1**
Blood Pressure							
Systolic.....Av. (mm.)	**128**	**106**	**161***	**106**	**117***	**104**	**165**
Diastolic....Av. (mm.)	**80**	**71**	**81***	**66**	**72***	**72**	**110**
Pulse Rate Av. (per min.)	**72**	**56**	**80**	**64**	**61**	**81**	**84**
Respiration Rate Av. (per min.)	**20**	**12**	**11**	**14**	**15**	**13**	**16**
Temperature....(deg. F.)	**97.8**	**98.2**	**97.7**	**97.7**	**97.1**	**98.6**	**98.0**
Alveolar CO_2..Av. (mm.)	**46**	**43**	**37**	**41**	**39**	**42**	**33**
% less than 35 mm.....	0	0	50	0	0	20	100

#Value too high. Patient was nervous. Omitted in deriving average.
*A single case of hypertension influences the average unduly.

A closer analysis of the sub-groups is most informative. In the first (I-a), a single case, pituitary underactivity raises the tolerance 100 per cent. In the second (I-b), the depressing influence of the posterior lobe outweighs the upward thyroid tendency, and the result is a depression of moderate degree. In the dysfunctional Pituitary-Thyroid section (I-c), the Thyroid inhibition of the Pituitary depression is lessened, and the low level of —83 per cent is realized. In Group II, castration has lowered the tolerance to twenty grams, and the more powerful augmenting power of posterior lobe failure on assimilation capacity raises the tolerance over 100 per cent above prediction.

TABLE IX

Galactose Tolerance

Group	Case Number	Function			Galactose Tolerance			Group Average
		P (post.)	T	G	Normal	Observed	Deviation	
I—a	B- 37	—	—		30	60	+100	+100
b	B- 18	+	—		40	30	— 25	— 38
	B- 532	+	—		40	20	— 50	
c	B- 141	+	±		30	5	— 83	— 83
	S- 568	+	±		30	glycosuria	?	
II—a	B- 659	—		—	20	60	+200	+110
	S- 744	—		—	20	30	+ 50	
	S-1327	—		—	20	40	+100	
	S-1343	—		—	20	40	+100	
	S-1669	—		—	20	40	+100	
*III—a	S- 686		—	—	40	30	— 25	+ 13
	B- 109		—	—	20	20	± 0	
	B- 599		—	—	20	30	+ 50	
	B- 662		—	—	20	30	+ 50	
	B- 976		—	—	30	30	± 0	
	S-1843		—	—	20	20	± 0	
b	S- 179		±	—	40	10	— 75	— 19
	S- 230		±	—	20	glycosuria	?	
	S- 988		±	—	20	10	— 50	
	S-1023		±	—	20	20	± 0	
	S-1069		±	—	20	30	+ 50#	
IV—a	B- 164	+?	±	—	40	10	— 75	

*Note inclusion of Case B-976.
#Marked Thyroid failure under heavy medication at time of test and included in dysfunctional group for this reason.

Unweighted Averages

	Hypo-	Dys-
P + T	+100	—60
P + G	+110	—
T + G	+ 13	—19
P + T + G	—	—75

Turning to Group III—Thyroid and Gonad—the first case in sub-group "a" is a possible functional ovarian failure superimposed on a hypofunctional thyroid. This determines a slight lowering from the normal level. The second and sixth cases were castrates with a functional hypothyroidism that did not affect the tolerance, while in the third and fourth the magnitude of the thyroid depression raised the tolerance 10 grams above the level determined by the castration. The fifth case, the only male in the entire series, shows a normal tolerance, the thyroid failure not being sufficient to raise the assimilation limit, and the castration being devoid of influence on this function. The divergent tendencies are more variably expressed in the individual members of Group III-b, which is not entirely uniform in its composition. For example, in Case S-179, a functional gonad failure and thyroid dysfunction (surgical), the one influence supplements the other and produces a level 75 per cent below prediction. On the other hand, Case S-1069 by castration has a predicted level of twenty grams, but the superimposed thyroid failure raises the assimilation limit to thirty, or an increase of 50 per cent. This latter subject was under drastic thyroid medication and in spite of this the basal rate was still —12 per cent. As was discussed at some length in the thyroid paper, we have some reason to believe that this gland produces more than one active principle, and that while the energy regulating hormone —thyroxin or something similar—may be supplied in exact measure, another agent which influences the carbohydrate tolerance may be simultaneously either in excess, equal amount or deficit. The other tolerances observed in the group are those which could be predicted from the algebraic sum of the several agencies operative.

This concludes the presentation and discussion of the more salient points elicited by the laboratory examination. Many other observations were made with each patient but their nature precludes presentation in summarized tabular form.

To conclude this discussion, a few of the characteristic influences are sufficiently salient to manifest themselves even under the inhibiting conditions of tabular presentation. These are, in the main, the relative values resulting from comparison with standards absorbing individual variation or, as in the case of the galatose tolerance, where additive relations exist. The results of the special clinical observations of the Consulting Staff adapt themselves even less well than do the laboratory data to the tabular form of presentation.

The characteristic features of disturbance of the individual glands has already been adequately covered in the previous papers. While the protocols of each case will be given later in the paper, a few of the clinical data may, for the sake of convenience, be collated for discussion. In the main, such analysis is unprofitable, as the factors of variation are too many to make collective consideration significant. The exceptions will be dealt with in the next section.

Part II

Note has already been made of the relatively greater age of this group at the time of first admission to the Clinic. Likewise, the age of onset of the chief complaint, as given, falls in a later decade than was the case with the uncomplicated endocrinopathies. The significant data are collected in Table X.

TABLE X.

AGE

Decade	Age of Admission	Onset
11-20 years	1	2
21-30 years	0	5
31-40 years	6	7
41-50 years	8	5
51-60 years	5	2
61-70 years	1	0

The first is a dependable datum, but the second is largely influenced by subjective factors that cannot be evaluated.

The average duration of the chief complaint in the group is ten years, a value, as will be shown in a later table (XIII), exceeding the dates of the thyroidectomies but falling short of those of the castrations. The chief complaints are varied and in most of the cases more than one is presented.

Fatigue in this group, as in those of the uncomplicated endocrinopathies, is a major symptom. Half presented it as a chief complaint, and practically all of the remainder mentioned it as a secondary disability.

Pain appeared as a major ailment in one-third, and as a contributory factor in practically all of the remaining cases. It was rarely confined to a single area. The frequent incidence of pain as a symptom has already been noted in the Gonad paper, and it must be remembered that two-thirds of this group had been castrated.

TABLE XI

CHIEF COMPLAINTS

Fatigue	11
Pain	7
Obesity	4
Headache	4
"Nervousness"	4
Dyspnoea	3
Anaesthesias Paraesthesias	3
Skin Eruptions	3
Deafness	2
Digestive Disorders	2

Four patients complained of obesity and two more exhibited it in a marked degree. In view of the usual association of obesity with endocrine failure, an analysis of this group is interesting.

TABLE XII.

OBESITY

Group	Obese > +15%	Normal +15% to —10%	Thin <—10%
Pituitary-Thyroid	2	3	0
Pituitary-Gonad	1	4	0
Thyroid-Gonad	3	5	2
Total	6	12	2

Case B-164 has been omitted.

While the normal limits adopted are perhaps too liberal, of this group three were above, three equalled, and six were below prediction, a fact offering further emphasis on the unwisdom of assuming that endocrine failure necessarily determines overweight. The dysfunctional thyroid case might be assumed to produce emaciation, but two of the six obese patients, a just proportion, fall in this group. Headache, unassociated with menstruation and "nervousness" were or had been common complaints. The frequency of this first symptom in the endocrinopathies has recently been stressed by Drury (9). The other complaints as offered are generally recognized as frequently associated with endocrine disease.

Four of the patients gave a family history of endocrine disorders, diabetes and thyroid disease being mentioned.

In their own histories a principal point of interest lies in the surgical events which had determined the pluriglandularity of so large a portion of the group.

TABLE XIII.

Operation	No.	Date (Average)
Thyroidectomy	4	6 years previously
Single Oöphorectomy	2	7 years previously
Double Oöphorectomy	14	12 years previously

Of the thyroid subjects, two had had more than one operation, while several of the castrates had had one ovary removed prior to a second and complete operation.

The thyroid status of the group at the time of admission showed four operated cases as noted above, fourteen with no evidence of thyroid enlargement, and three with small goiters, one in each of the three major groups.

TABLE XIV-a.

MENSTRUAL HISTORY

(a) *Onset*

Year	Number
10 years	1
11 years	3
12 years	4
13 years	5
14 years	4
15 years	2
16 years	1
17 years	1

With so general an involvement of the organs of generation, the facts of the sexual histories are very informing. Almost all of the group had passed a menopause, artificial or natural, but the previous menstrual histories can be collected for presentation.

The relative values here would compare with those of any other group selected at random. Two-thirds fall within the conventional span of 12-14 years, and but three show a really early or delayed onset. No racial influence could be traced in these latter as they were all of English birth or origin.

TABLE XIV-b.

(b) *Character*

Rhythm		Flow		
		Increased	Normal	Diminished
Irregular 8	Increased	0	2	0
	Diminished	2	1	0
	Both	1	2	0
	Total	3	5	0
Regular 13		1	11	1
	Grand Total	4	16	1

Normality of function seems to be the rule with eleven patients both regular in rhythm and normal in amount, while two more are normal in rhythm and five more in amount. Three show the conventional irregularity of thyroid disease, the others scatter with but one showing a diminished flow. This is somewhat striking in view of the large number subsequently operated upon. Apparently, cystic degeneration—a common cause for castration in this group—does not lessen the flow with the same frequency that it causes irregularity.

The reproductive power of the group is a natural sequel to the preceding.

One woman is omitted as she was married twice, conceived at least thirteen times, bore two children and had at least eleven induced abortions. The second child was delivered by Caesarian section and at this time a pan-hysterectomy was performed.

The figures given above are extremely interesting in view of the endocrine status of the group. All of them were endocrine cases although not all were certainly pluriglandular. In a larger group (100) drawn from the gonad series, 31 per cent were sterile and 10 per cent had conceived, only to miscarry; in other words, 59 per cent only had been productive. In this group 86 per cent of the women capable of bearing children had done so, the 14 per cent sterile comparing well with the average (10-12 per cent) given by Reynolds and Macomber (10) as a fair value for unselected groups.

TABLE XV.

FERTILITY

Unmarried	5	
Castrated before marriage	2	
Total		7
Sterile	2	
Productive	12	
Total		14
Of 11 married women:		
Children	18	
Miscarriages	8	
Abortions (induced)	1	
Tubal Pregnancies	2	
Total Conceptions		29

An inference here would be that the endocrine condition was established in most of the cases in adult years after maturation and opportunity for exercise of a normal procreative function. The previous histories and ages of onset, as given, would support this idea. Of the five subjects without surgical complication, two were unmarried, one had borne five children with one miscarriage, one had conceived but terminated the pregnancy voluntarily, and the third was a young girl, 19 years of age, who had had one miscarriage in her year of married life.

While one must be conservative in the interpretation of end results in a series of cases presenting such numerous evidences of conjugate endocrine involvement, the foregoing analysis certainly does not offer a direct support to the theories of pluriglandular involvement in childhood so frequently adduced to explain developmental aberration.

One other minor point may be touched upon. In the earlier papers emphasis has been laid on the frequent incidence of tonsil involvement. In the present group six had been operated once or more, four had diseased tonsils, while eleven were normal as regards the tonsils. The percentage of positive cases here falls somewhat behind the other groups but is still at a significant level.

As was noted earlier in the paper, the very nature of the cases composing this group seriously inbibits collective presentation. We have felt it better, in the interest of our readers, to conclude the discussion with a brief protocol of the case of each of the patients here included. The limitation of space determines brevity but effort has been made to include the salient details.

PART III

CASE PROTOCOLS

GROUP I-a. PITUITARY FAILURE AND THYROID FAILURE.

CASE B-37. This patient was first seen in January, 1923. She gave as her chief complaint, excessive somnolence. She had had an attack of influenza at the time of the epidemic and her seizures of "uncontrollable sleep" began shortly afterward. There was no warning of the seizure but in the midst of sewing, reading or even talking the eyes closed and to outward appearances she would lose consciousness. She maintained that she was conscious of what went on about her during these attacks. The attack usually lasted from 10 to 15 minutes, they showed no periodicity and they occurred at intervals varying from days to weeks. The patient was also extremely obese but did not offer this as a complaint. Her previous hospital examination elsewhere had led to a diagnosis of pituitary failure but the patient had not benefited from a brief course of treatment which had been subsequently given. The family history gave heart failure as the cause of the father's death. There were six living siblings of whom one, was a surgical castrate who had also been studied by us. Cancer was recorded in the earlier generations. The patient had had measles and chicken-pox in childhood and typhoid at the age of 34. She had had attacks of arthritis at different times during her adult life. She reported headaches only at the time of her periods and a negative gastro-intestinal and genitourinary history. Of late years she had had some dyspnoea with palpitation and also reported occasional swelling of the feet and ankles. She had matured at 13 and believed her periods to be fairly regular. At the age of 51 the menstrual function was apparently unimpaired and she had a 4-day period shortly before entering the hospital. Her highest weight she believed to be about 250 pounds. She weighed about 240 pounds at the time of entrance. The patient was a heavy coffee drinker, when at home averaging nine or ten cups a day. The physical examination showed a well-developed but very obese woman in middle life, her obesity tending toward a girdle distribution. The head was covered with a moderate growth of coarse dark hair; elsewhere there was no excessive pilosity. The teeth were small and irregularly spaced. There was a roll of fat around the neck and no enlargement of the thyroid could be demonstrated. The breasts were very large and pendulous, the lungs and the heart, apparently normal. The abdomen was very obese which prevented an entirely satisfactory examination. There were numerous varicose veins on the lower extremities and a small tumor growth in the lateral aspect of the right knee just outside of the patella. The knee jerks were somewhat sluggish but equal. The urine examination showed a volume of over 2½ liters; the elimination was poor, balance fair. Albumin was reported but no other abnormalities. The sediment was normal. The protein intake as gauged by the nitrogen elimination was ample and the partition formula of the latter within normal limits. The blood showed a high haemoglobin and red count, a marked lymphocytosis (60 per cent) and was otherwise normal. Chemically the blood showed an absolutely high uric acid and a slightly high blood sugar, the latter probably due to an emotional response as the venipuncture was difficult and painful. The alveolar carbon dioxide was a high normal. The serological tests were negative. The sugar tolerance was increased 50 per cent above prediction, a dose of 60 grams of galactose being necessary to produce a positive response in the urine. The patient was 81 per cent above her predicted weight, while the lung capacity was less than half that predicted by the Dreyer standard. The basal rate was —34 per cent, the pulse and temperature being substantially normal, the blood pressure relatively somewhat low. A neurological examination gave substantially normal findings. It gave no evidence of organic lesion. The patient was somewhat dull mentally without exhibiting any psychotic element of significance. The eye examination showed normal fields, blind spots slightly enlarged and apparently normal discs. A radiogram of the aortic arch showed a thickened wall. The remaining chest X-ray findings were normal as were those of the skull, sella and sinuses.

Discussion: The picture presented by this patient was clearly endocrine but the actual gland or glands at fault were not easy of determination. The large volume of the urine, the high blood uric acid, normal nitrogen partition, the somewhat low blood pressure, normal pulse rate, 'phthalein test, and relatively large increase in the tolerance threshold were all suggestive of pituitary deficiency. In addition, the type of distribution of her obesity, the history of her presenting difficulty, and a number of other points elicited in the physical examination and history were confirmatory. On the other hand, the magnitude of the deviation of the basal rate was greater than we have ever associated with uncomplicated pituitary failure. The lack of excessive hair growth and other points of a like nature, tended to emphasize the thyroid element. At the time of the examination it was felt that this case might properly be classed as a true pluriglandular condition with lowered functional activity both of the pituitary and the thyroid. That a therapeutic test might be given, the patient was placed on thyroid medication alone with observations made at fairly frequent intervals. The basal rate improved somewhat, reaching in mid-June a level of —19 per cent. The weight was unchanged, the pulse remained in the mid-seventies, and there was no effect on the sugar tolerance. The thyroid dosage at this time was somewhat variable as the patient's cooperation was not complete. Her average intake, however, was of the order of 5 or 6 grains per day. Pituitary medication was added to her variable thyroid intake and in October of the same year (1923) a partial study was made. The urine volume had dropped somewhat but was still ample, averaging about 1800 c.c. Albumin persisted. The earlier normal residual nitrogen remained unchanged. The earlier lymphocytosis was at the same high level. Body weight had decreased but three kgm., and practically all of the other findings were at the earlier level. Two changes, however, were recorded. The basal rate had become normal and the sugar tolerance had dropped to 50 grams. The patient was discharged with the recommendation to continue both the thyroid and the pituitary treatment and was seen again in March of 1924. There was reason to believe that again she had not been consistent in following her treatment but equally that she had taken a good deal both of thyroid and of pituitary substances. The urine presented the same general picture as did the blood chemistry and blood morphology. The patient had lost some 10 kilograms more but was still markedly obese. The basal rate at the time of the study was —12 per cent with a pulse of 70. The "sugar tolerance" could not be secured.

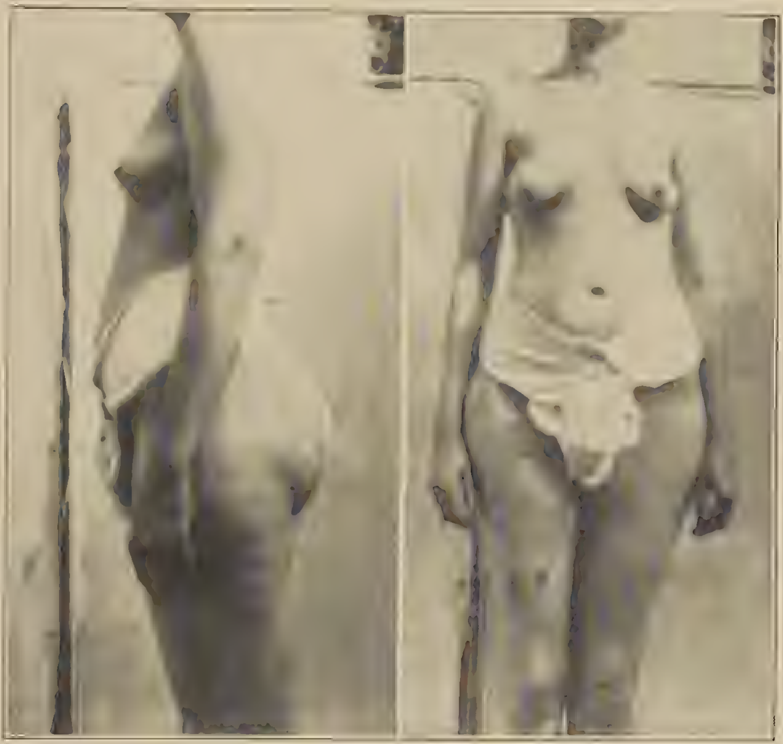
This patient represents one of the few cases in our very long series in which, seemingly, there was simultaneous primary involvement of two endocrine glands. On thyroid medication alone the patient showed but little change, while her history showed that her earlier pituitary medication had been equally ineffective. The combination of the two was apparently necessary to normalize the basal rate and induce such changes as were recorded. Her attacks of drowsiness had become less during the fifteen months but as they had been showing a lengthening interval before we studied the case, it is not legitimate to ascribe this improvement certainly to the medication. The patient's relatively slight loss of weight was undoubtedly ascribable to her unwillingness to curb her large appetite. She was studied early in the present series of investigations. Certain laboratory procedures which have since become available and, more importantly, a number of skilled opinions in the specialized fields of medicine were not available at the time of this study. Shortly after the last observation in 1924 the patient moved to the far West and we have had no further news of her since that time. From the data available, recognizing its incompleteness, we feel constrained to report this patient as presenting a genuine pluriglandular condition.

GROUP I-b. PITUITARY DYSFUNCTION WITH THYROID FAILURE.

CASE B-18. This patient was admitted in 1922 for a study of her endocrine status. She was a woman of 35, nearly 6 feet 3 inches tall, who complained of an anaesthesia of the middle third of the body accompanied by incontinence of bladder and rectum. Three years previously she had been admitted for retention of urine and the use of the cystoscope revealed her anaesthesia in this region. Under treatment the condition cleared up in about 3½ months. When readmitted in 1922 for this study, she stated that she had been unconscious of the passage of feces since her illness three years before, and that a similar condition existed in regard to urination. It seemed probable that some degree of the anaesthesia of the anterior portions was of much longer duration, since she had never been conscious of the menstrual flow escaping from the vagina. There had never been any sex urge.

A second complaint was recorded, namely, back pain, from which she had suffered for about 10 years although she gave a history of weak back from the age of 10. She had been under orthopedic care and had worn various supporting appliances, from which she derived some benefit, for a number of years.

PLATE I



CASE B-18

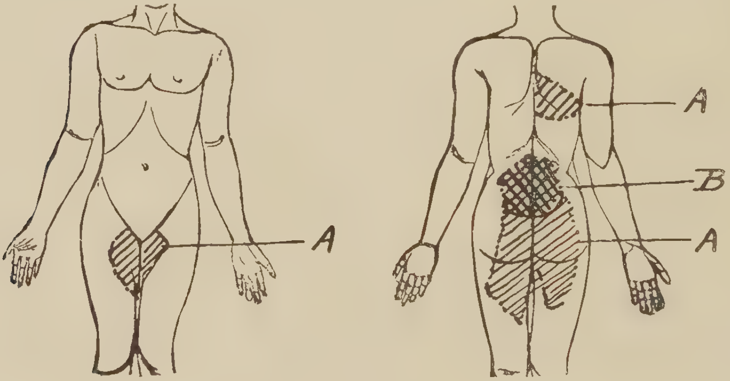
Both parents had died of diabetes and both were extremely obese, the father weighing 300 pounds and the mother 275 pounds. Her only sibling, a brother, had been 6 feet 4 inches tall and had recently died of advanced nephritis. The patient's own history included minor ailments and scarlet fever previous to her eighth year, at which time she had a severe attack of chorea, following which she had had to learn to walk again. Between the ages of 10 and 12 she grew to her present stature. The menses had been established at 13, and showed a somewhat shortened regular interval and scanty flow. The mental development had been wholly normal. The physical examination showed a very tall girl with low sitting height index

(0.50) and a tendency to girdle obesity not shown in other parts of the body which were somewhat underweight (see Plate). The head and body hair was somewhat scanty and of normal distribution. The thyroid was somewhat enlarged, the chest and abdomen normal. Rectal and vaginal findings were normal except for the anaesthesia. An earlier radiogram of the spine had shown no spina bifida; a very complete series of plates of the entire body showed no pathological changes in either the bony structure or the viscera. The neurological findings will be discussed in detail elsewhere. Summarized: three years previously, the tendon reflexes had been reported as normal; at the time of this examination the Achilles and knee jerks were absent. The anaesthetic areas are shown in the accompanying chart (q. v.).

The urine volumes were normal, elimination and balance good. Albumin was present; the remaining findings, including the nitrogen partition, were normal. The blood morphology was normal, the blood chemistry equally so, and the serological tests were negative. The 'phthalein elimination and CO_2 level were normal. The sugar tolerance was slightly depressed, the "vital capacity" comparisons substantially normal. (The low sitting height index has already been noted.) A series of basal rate determinations gave values between —20 per cent and —25 per cent with definitely low blood pressure and slow pulse. A urea curve was normal.

Discussion: With the patient's bodily habitus and history, the first thought here would be of an earlier over-active pituitary passing through a functional involution state and presenting the common dysfunctional formula. The sugar tolerance would harmonize with this idea, as would the observed level of the basal rate. The eosinophilia and high blood uric acid are lacking, and the blood pressure, pulse rate and alveolar CO_2 are at levels more suggestive of thyroid failure. The observed basal rates were as low as —25 per cent, a somewhat extreme value for anterior lobe failure—and it was questionable if the patient were ever in a truly basal condition. The thyroid enlargement was not necessarily meaningful as it is a not infrequent report in cases of uncomplicated pituitary disease, to say nothing of its frequency in normal and non-endocrine conditions. In other words, there were evidences of a possible true pluriglandular

PLATE II



CASE B-18

state in which the pituitary was the earlier and recessive, and the thyroid failure, the later and dominant element. On this basis a tentative diagnosis was offered and thyroid medication instituted. The anaesthesia gradually cleared up and the incontinence disappeared. This response to the thyroid medication is felt to offer some support to the initial diagnosis. The later history of this subject will be reported later; none of its events have thrown any more light on the basic, underlying endocrinopathy. In fairness, we feel that it must be reported as a pluriglandular involvement, although the pituitary element was principally represented by structural residua.

Case B-532. The patient was a woman of 33 referred to this Clinic primarily for obesity. She had been married for 10 years during which time she has six pregnancies, the first resulting in a miscarriage at three months and the other five in viable children three of whom, however, showed a definite retardation in mental development. At the time of her marriage the patient was not strikingly obese. After this event, however, she began to increase weight, and after the completion of her fourth pregnancy she weighed 160 pounds. She then began to gain more rapidly and in the course of 5 years reached nearly 250 pounds. By rigorous dieting she reduced herself about 40 pounds in the course of a year, but prior to admission had begun to gain again and weighed 215 pounds when we first saw her. Both of her parents were said to be extremely nervous. She had two brothers who were well and apparently normal. She reported one aunt who was a diabetic and extremely obese. Of her own history she reported the usual minor ailments of childhood together with scarlet fever, influenza at the time of the epidemic, and pneumonia in 1922. A breast abscess was lanced in 1917. She had occasional headaches when fatigued and what she described as neuralgic headaches when her teeth were in poor condition. This latter condition was seemingly one of recurrence and there was a long history of dental troubles. She complained of vertigo during her pregnancies. Within the past three years there has been much thinning of the hair on the vertex. She noted optic fatigue, some loss of hearing, frequent severe attacks of rhinitis and, she believed, some nasal obstruction. The cardiac history was substantially normal. She had been fatigable for a number of years and this condition was accentuated during her pregnancies. After each confinement there was a brief period when the patient had night sweats. Experience had shown that unless food were taken shortly after arising there was a tendency to nausea. The periods began at 13, were regular, and apparently normal in amount. She had had recurrent attacks of pimples on the breasts. For many years she had had some intermittent pain in the legs and knees. There was also stiffness of the neck, and at the time of the breast abscess there was "articular rheumatism" in all the joints. Of later years she had experienced numbness and cramps in the legs and tingling in the hands associated with coldness of all extremities. There had never been any evidence of mental impairment, she having made excellent records at school and college. The physical examination showed a definitely obese woman with a marked tendency toward girdle distribution. The eyes and ears were normal, the tonsils slightly enlarged and cryptic, teeth in poor condition, no apparent thyroid enlargement, heart and lungs normal, abdomen markedly obese, arms and legs large, ankles possibly slightly edematous; the hands, wrists and feet were small. There was a slight scoliosis, a slight cervical adenopathy; the skin was somewhat hypertrophic and dry. Routine neurological findings were normal. The urine was normal in amount;

elimination and balance were poor. One specimen showed albumin and all, a trace of sugar; the sediments were normal. The nitrogen partition determination showed an elimination indicating a somewhat low protein intake; the partition formula was normal. The blood showed a marked relative lymphocytosis (47 per cent) and a 3½ eosinophilia. The blood uric acid was above the normal level, the blood sugar normal. The serological findings were normal. The 'phthalein elimination was somewhat low. The patient's sugar tolerance was half the level normal for a woman of her age and sexual status. By the Dreyer standard she was 38 per cent overweight, but her obesity was actually in excess of this as the sitting height index was 0.55, a value well above the normal. Her lung capacity was slightly above prediction. Two independent basal rate measurements gave a value of 44 per cent below prediction, with slow pulse and a blood pressure just below 100. Her alveolar CO_2 was normal. X-ray findings of the heart, lungs and mediastinum were all normal; of the teeth showed much alveolar absorption and several periapical abscesses. A neurological examination gave no postive neurological findings. A nose and throat examination demonstrated a slight septum deviation not sufficiently important to warrant interference. A cardiogram showed a slight sinus arrhythmia and low voltage but was otherwise normal; this finding was confirmed by a heart consultation. The eye grounds showed yellowish discs, enlarged blind spots, and some symmetrical contraction of the form and color fields.

Discussion: The majority of the findings in this case were entirely harmonious with the general picture presented by a case of pituitary dysfunction. The normal urine volume, slight glycosuria, the normal nitrogen partition formula, the slight eosinophilia, high blood uric acid, lowered galactose tolerance, normal lung capacity, high alveolar carbon dioxide, integrate to form a picture of pituitary disease. This conclusion is supported by a number of points in the history and physical examination. On the other hand, the basal rate was at a level which had been observed by us only in thyroid failure; with this was a blood pressure definitely lower than that usually recorded in pituitary disease, and also a slow pulse. A urea curve showed a normal shape with somewhat depressed elimination, and the 'phthalein test was somewhat low—factors again more suggestive of thyroid failure. Here again the various data, while defining unmistakably an endocrine disturbance, exhibit magnitudes and directional relationships which it would be difficult to associate with the uncomplicated failure of a single gland. The patient was put on thyroid medication. Four months later she had lost less than 2 kilograms, exhibited an unchanged blood pressure and pulse rate, and a basal rate still 27 per cent below prediction. Thyroid medication alone was continued for three more months without producing any change, the patient gaining 0.2 kgm. in weight and showing a basal rate of —23 per cent. Pituitary medication was then added to the thyroid and later reports show a definite improvement, although we have no laboratory records of later basal rate measurements.

This case like that of B-37 is seemingly one of simultaneous involvement of both pituitary and thyroid. The pituitary formula is not the same, as in this case the posterior lobe exhibits a definite overactivity, while in the first a bilobar failure was the condition. With the data available and such knowledge as we possess of endocrine disease at this time, diagnosis of a pluriglandular condition involving both the thyroid and the pituitary is seemingly the only one which is warranted.

GROUP I-c. PITUITARY DYSFUNCTION WITH THYROID DYSFUNCTION.

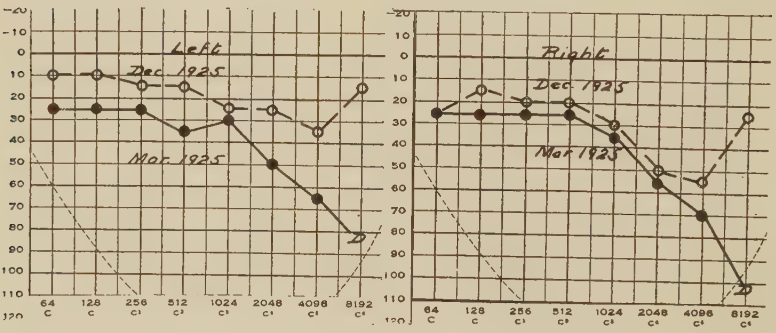
CASE B-141. The patient's chief complaint was of a steady increase in weight coupled with an increasing dryness of the skin and an intermittent flushing of the chin, cheeks and upper chest. Some 17 years previously the patient began to develope a disturbing nervousness and to lose weight. This condition continued progressively until 1911 when a diagnosis of hyperthyroidism was made and an operation performed. Two years later there was some recurrence of the earlier symptoms and on her own initiative the patient instituted a course of thyroid medication. Somewhat later this procedure was approved by her physician. The thyroid therapy was subsequently discontinued and a year before the patient was admitted to this Clinic she began to develop the symptoms which ultimately led to her reference here. She was a woman well above the average height; one of her siblings was 6 feet 4 inches tall at the age of 14 and was mentally deficient. The father had diabetes for a long time prior to his death; the mother had had Graves' disease, was operated upon and developed myxedema before her death from heart failure. Eight siblings were alive and well. The patient's own history showed only the minor ailments of childhood outside of the events recorded above. She had been married for 21 years. Her first pregnancy terminated in a miscarriage. Subsequent examination disclosed a retroversion of the uterus for which the patient was operated upon. A second pregnancy terminated at full term but the child was stillborn, delivery being instrumental. A third pregnancy resulted in a viable child which died, however, two years later of meningitis. The fourth and last pregnancy ended in a miscarriage at three months. The patient matured at the age of 10 and the menstrual function was normal and regular up to that of 15. During this interval she grew very rapidly and at the age of 14 was 5 feet 11 inches tall and weighed 170 pounds. From 15 years of age, to the time of her marriage her periods came every two weeks and were very copious. With marriage, the interval and amount again normalized. When seen by us at the age of 51 she had just passed an uneventful menopause. The patient gave a history of severe headache with her pregnancies and during her attacks of hyperthyroidism. She was at no time fatigable—in fact mentally and physically she was distinctly above the average. She had diarrhoea in the summer time but was never constipated. The remaining history was not remarkable. Physical examination showed a tall woman with high color, not excessively overweight. The bridge of the nose was underdeveloped; the teeth showed some dental attention, there was a slight residual thyroid enlargement, heart and lungs were normal as were the routine neurological findings. The skin on the lower part of the body was dry and scaly. The urine volume was normal, elimination and balance good; a small amount of sugar and increased indican were reported. The sediment was not suggestive. The nitrogen partition contained a high residual fraction. The blood showed a definite lymphocytosis but was otherwise normal. The serological tests were negative. Blood chemistry was normal; the 'phthalein test somewhat low. The patient had a greatly depressed sugar tolerance, a dose of 5 grams of galactose per os being sufficient to produce a trace of galactose in the urine. She was 14 per cent overweight and had a normal sitting height index. The lung volume was 25 per cent below prediction. Alveolar carbon dioxide was slightly low. The basal rate was —6 per cent with a somewhat hypertensive level of the blood pressure and slightly slow pulse. The eye findings were substantially normal; examination of the fundus showed some vascular sclerosis. The pelvic examination demonstrated residua of her earlier childbearing but was otherwise normal. Radiography showed the skull and sella to be normal; the aortic arch was prominent; otherwise the chest was apparently normal.

Discussion: While a complete resolution of this case involves a certain amount of speculation and surmise, certain points would seem to be fairly established. That the patient presented a pituitary aberration in adolescence, there can be but little question. A residuum of the posterior lobe overactivity is manifest in the very low galactose tolerance threshold. Her relatively normal basal rate must be regarded as due to the sum of the thyroid and pituitary influences. That there was an earlier thyroid overactivity must, we believe, be accepted. The operation had unquestionably lowered this activity but to what extent, it can not with certainty be said. If the pituitary disease had terminated in the usual dysfunctional formula, then the anterior lobe would be below a normal level, and this could be compensated by a residual slight overactivity of the thyroid. But it must be remembered in interpretating all basal rates that the values observed are maxima and that the true basal rate may well be definitely below that observed. The patient was an extremely intelligent woman with a sound philosophy of life. In spite of her previous medical contacts which had involved basal rate determinations she was a little nervous although controlled at the time of this test. As we saw this case a probable earlier hyperactive pituitary had in part undergone a functional involution, leaving a characteristic dysfunctional formula. Superimposed upon, and independent of, the pituitary condition a possible hyperthyroid activity had supervened. Operation had produced a dysthyroidism of relatively minor moment. If there were aberrant thyroid activity it would presumptively be on the side of some residual hyperfunction—at least of that element in the gland which influences oxygen requirement. Obviously, medication for such a condition must stress the potential pituitary state and ignore the probably less significant thyroid. There is certainly no evidence presented that would warrant further thyroid operation. On this basis anterior lobe medication was recommended and subsequent reports both from the patient and from her referring physician recorded a marked general improvement. This case presents a type of pluriglandularity in which one endocrinopathy is superimposed upon a second which had antedated it, usually by a considerable interval. The general picture, here, in the main reflected the dominant and initial endocrine disturbance. The thyroid element was an added effect, was not adequate to produce marked changes in the disease picture engendered by the primary endocrinopathy, and in its present status derived, in some measure at least, from the earlier surgical intervention. A possible alternative explanation would have been a thyroid failure of surgical origin complicating a still earlier existing bilobar hyperpituitary activity. Had this been the case the exhibition of anterior lobe medication would presumably have produced unfavorable results on the patient's symptoms. The marked betterment which she reported leads us to feel that the first hypothesis discussed offers the larger measure of probability.

CASE S-568. This patient was referred to us for deafness, of which she had been conscious for the past 3 or 4 years. The progress had been gradual and the severity somewhat variable and influenced by the patient's nervous condition. She had not experienced tinnitus nor did she show paracusis. Some years prior to her recognition of the condition she had been under a severe nervous strain and she felt that this, in part, might have been operative in determining the condition. A brother and an uncle were both deaf. She reported several cases of cardio-renal disease in near relatives. The patient's own history showed the usual minor ailments of childhood, as well as diphtheria and scarlet fever. She had the influenza in 1918 and several attacks of tonsillitis prior to a "T. & A." operation three years previously. She was occasionally constipated and when in this condition she developed nausea and vomiting. The menstrual history showed a normal onset and an uneventful history including the menopause which latter had transpired some two years before. She had been married for 7 years with one pregnancy ending in an induced abortion. She complained of dizzy spells which came at irregular intervals. The condition would last for a month or two and then she would be free for perhaps a year. Her social history included several events calculated to produce a marked degree of nervous tension. The patient was nervously unstable and markedly fatigable. A study carried out some time previous to her entry into this Clinic defined her deafness as of a toxic type and assigned the teeth, gastro-intestinal tract and, at the time of that examination, the menopause, as contributory factors. Prior to her admission the patient had experimented with small doses of thyroid and of ovarian preparation without noticeable benefit. Physical examination showed a well developed, slightly obese woman, of 55; there was a suggestion of exophthalmos and a slight edematous pouching beneath the eyes; several teeth were missing, and the remainder showed much dental attention. There was a slight struma, a slight pleuritic rub was heard in the right chest, the heart and abdomen were normal, and skin on the extremities dry and scaly. The fat distribution suggested the girdle type. The hair distribution was normal. The urine showed a normal volume, good elimination and poor balance; a trace of sugar was reported; the sediment was normal. The nitrogen partition implied an inadequate protein intake and gave a high residual nitrogen. The blood showed a somewhat low haemoglobin, a slight leukopenia, a relative increase in the lymphocytes, and a 5 per cent eosinophilia. The blood was normal in chemical composition with the uric acid relatively high. The serological tests were negative. The phthalein output and alveolar carbon dioxide were normal. She was 12 per cent overweight and nearly 30 per cent below her predicted lung volume. A fairly satisfactory basal test gave —25 per cent, a somewhat rapid pulse and normal blood pressure. The radiographic plates showed a large sella, 16 mm. x 15 mm., and a negative chest and skull. The eye examination disclosed yellowish discs, slightly enlarged blind spots, and a very slight cutting of the form field. The audiogram, herewith reproduced, showed a marked loss of hearing in the upper tones in both ears, and some diminution in the lower register. The cardiogram was normal.

Discussion: The case presented several points of interest. In the first place the rapid pulse, low basal rate—for the value recorded was undoubtedly above the truth—enlarged thyroid and suggestion of exophthalmos were suggestive of a thyroid failure. Equally, the lowered sugar tolerance, eosinophilia, eye findings and enlarged sella were more in conformity with a pituitary condition. We felt that the inconsistency between the sugar tolerance and the magnitude of the basal rate could best be explained by the assumption of the existence of a true pluriglandular condition. Analysis of the entire case, however, with proper weighting of the several differential factors led to the conclusion that the pituitary influence at the time of the examination was distinctly less than that of the thyroid. On this basis it seemed desirable to attempt a therapeutic test with thyroid medication alone, and with the patient's consent this was done. The results of this treatment, which had been carried on since that time, had, in the main, been very satisfactory. The patient's hearing, as shown by the audiograms and by clinical tests, has definitely improved. A considerable amount of nervous instability has disappeared, and from the clinical standpoint there has been a definite and unmistakable improvement. It has been found expedient in this case to supplement the thyroid extract with some thyroxin and she has also received courses of treatment with anterior pituitary. These latter, however, have been of brief duration and we are uncertain if this latter medication has played any real part in the patient's betterment. We have recorded the case but without marked enthusiasm as one of pluriglandular involvement. It is possible that this case is essentially one of thyroid dysfunction and that the pituitary evidences were apparent rather than real.

Plate III



Case S-568

Many of the data suggesting a pituitary involvement could equally derive from a diseased thyroid in a transition state between an initial hyper- and final hypo-activity. As was noted in our earlier paper on the thyroid (3), patients presenting this condition are not uncommon. Another possible explanation of the lowered sugar tolerance and other pituitary evidences could lie in the existence of a low-grade liver dysfunction, a condition of which certain portions of the patient's history are suggestive. While we feel that the diagnosis of uncomplicated thyroid dysfunction holds the largest measure of probability, the data as presented, in fairness warrant the tentative inclusion of this case in the pluriglandular group.

Group IIa. Pituitary Failure and Ovarian Failure.

Case B-659. This patient was referred for a group of symptoms including dizziness, numbness of the hands, dyspnoea, palpitation, and pain in the left costal border. She was a woman 65 years of age who, at the age of 35, had had one ovary removed and at the age of 50, the uterus and remaining ovary. Seven years prior to admission, the patient then being 57, she developed intermittent attacks of numbness and tingling in the hands. Various treatments were tried but without success. During substantially the same interval she had had pain along the left costal border which was also intermittent. Dizziness, palpitation and dyspnoea had been of but one year's duration. There was a familial history of tuberculosis and of cardio-renal disease. During the patient's 13 years of married life she had never conceived although contraception was not practiced. For the 34 years preceding her admission she had worked very hard. She reported all of the minor ailments, together with diphtheria, scarlet fever, tonsillitis, and pleurisy. She recounted only the two operations noted above. Recently she had developed headaches but for many years had been troubled with pain and lacrimation in both eyes, coupled with failing vision. She was deaf in the left ear and often had pain in the right. Most of her teeth had been removed. She was markedly constipated; there was some nocturia. From her history, although her statements were not completely informative, it seemed probable that her husband had infected her with gonorrhea during her married life. The menses were established at the age of 11; the periods were regular but were always scanty. An uneventful menopause antedated her hysterectomy by five years. During the last few years she reported a steady increase in weight. Physical examination showed an obese woman in the mid-sixties, with a moderate amount of grayish-white hair, that on the body being normally distributed. The features were full and coarse. The left ear was practically deaf. There was slight hearing power in the right. The few remaining teeth were in fair condition. The thyroid was not enlarged. Heart, lungs and abdomen were substantially negative. The peripheral vessels gave some evidence of arteriosclerosis. The routine neurological findings were normal. The urines were normal in volume, the elimination good, the balance poor. One specimen showed albumin and all sediments showed much epithelial debris, but no casts were observed. The protein intake was barely at a maintenance level. The residual nitrogen fraction was high. The blood showed a slight leucocytosis with increase in the lymphocytes, while the oesinophiles were normal. The blood showed chemically, a slight upward tendency in all of the nitrogenous constituents. The serological tests were negative. The 'phthalein output was low. Galactose tolerance was 200 per cent above the patient's predicted normal. She was 52 per cent overweight and the lung volume was depressed about 40 per cent. The basal rate was —20 per cent in several concordant tests; her blood pressure was at the hypertensive level of 170/100. The pulse rates were in the lower sixties. The urea curve showed a fairly normal elimination. The alveolar carbon dioxide was normal. The radiographic study of the skull and chest was normal. A neurological report commented on the paraesthesias as reported coupled with the absence of any objective findings of significance. The heart examination determined an organ normal for her age and a tolerance for exercise reasonable for her weight. In the examiner's opinion there was no evidence of angina and he felt that the pain of which the patient complained might be due to mechanical causes connected with the lax and obese tissues. An audiogram showed marked but not complete loss of hearing in both ears. A Barany test gave normal responses. Pass pointing was within normal limits. The eye examination showed contraction of the form and color fields to about 30°. The discs were yellow, the left blind spot enlarged and in the right eye a scotoma was demonstrated signifying involvement of the paramacula fibers.

Discussion: The patient's non-endocrine disease, consisting of her arteriosclerosis, hypertension, and early nephritis, obscures certain of the features of the general picture. The patient's history of surgery emphasizes one definite endocrine failure, while the laboratory findings indicate as well the presence of a bilobar pituitary failure. At the patient's age and with the non-endocrine elements in the case but little could be hoped from endocrine medication. Whole pituitary was recommended but contact was lost and we are not informed of the outcome with the case.

CASE S-744. This patient was a woman of 45 who was referred to the Clinic, presenting a progressive impairment of vision and a rapid decay of the teeth as her chief complaints. In regard to the first, she stated that she had worn glasses for 16 years, but during the last 3 or 4 years the vision had deteriorated rapidly. For many years she had been troubled with headache, which was usually frontal in character, although it occasionally involved the occipital region. These headaches occurred several times a week and were seriously disturbing. The patient had been married for 19 years, and during this time she had had five pregnancies resulting in three viable children and two miscarriages. Following the birth of the last child the teeth began to deteriorate. Six years ago both ovaries had been removed. The family history showed that the mother suffered from similar headaches; the father was diabetic and, of two living siblings, one was a chronic invalid. Three brothers and one sister had died before the age of one year. The patient's own history showed only measles in childhood, a sinus operation, an appendectomy at the time of her castration, and a dilatation and curettage after each of her miscarriages. She had been in an automobile accident eight years previously and had lost consciousness for a few moments. She was not aware, however, of any subsequent ill effects. She stated that at the age of four years she had been blind for several weeks. She was ignorant of the cause of this condition, which apparently corrected itself spontaneously. She complained of occasional tinnitus, with no loss of hearing, constipation and a susceptibility to head-colds. The catamenia was established at the age of 15; the periods had always been irregular with increase in the interval, and the flow was scanty. Physical examination showed a small woman (5 feet), well developed and slightly over weight; the hair was coarse and slightly gray; body hair distribution normal. There was a slight divergent strabismus, the teeth showed much dental attention, the pulse rate was slow, and the remaining report, including the routine neurological examination, was not suggestive. The urine volume was normal, the elimination and balance good. The urinary nitrogen partition showed a somewhat low protein intake and a normal formula. She had had a slight secondary anaemia and a lymphoid blood with slight increase in the eosinophiles. The blood chemistry and phthalein test were normal. The serological tests were negative. The alveolar carbon dioxide was slightly below the normal. The patient was 12 per cent overweight and her lung volume was slightly below prediction. The basal rate was —23 per cent; there was some lowering in pulse, blood pressure, and body temperature. The sugar tolerance was 50 per cent above her predicted level. Radiograph of the skull showed a small, shallow and flattened sella. An eye examination showed yellowish discs and enlarged blind spots.

Discussion: To evaluate this case, it is, of course, essential to make allowance for the effect of her surgical hypogonadism. On this basis she presents evidences of a bilobar pituitary failure, which, added to the endocrine effect of her castration, determines a technical pluriglandular condition. Pituitary medication (whole gland) was advised.

CASE S-1327. The patient's chief complaint was of a skin eruption, from which she had suffered for several years. She also complained of severe headaches and a blurring of vision which followed spells of numbness on the left side. The patient had been married for 8 years and 3 years after marriage a tubal pregnancy necessitated the removal of one tube and the ovary on that side. Two years later an ovarian cyst was resected, and again 2 years after this the ovarian remnant and the uterus were removed. The skin eruption followed the first laparotomy, first showing as groups of small postules. For the preceding six months it had become more severe. Twenty-four years before, at the age of 11, the patient began to have spells of numbness, usually following violent exercise. At the same time a lateral hemianopsia developed, lasting for about fifteen minutes. The numbness would spread following this and last perhaps three-quarters of an hour and disappear spontaneously, leaving a severe headache as a residuum. Latterly, the spells of numbness had been confined to the left hand and left side of the body. These attacks at the time of admission were occurring at intervals of from a few weeks to several months. During them the patient never lost consciousness nor fell. The family history showed cardiac disease on the paternal side and was otherwise not significant. The patient had had various minor ailments and the influenza in 1918. She complained of occasional attacks of vertigo, some gastro-intestinal disturbance, urinary frequency during the day, and some nocturia. The catamenia was established at 13 and the history was not remarkable prior to her artificial menopause. The physical examination showed a well developed and well nourished woman in her mid-thirties. The eyes were normal, the teeth showed much dental attention, the tonsils were the seat of chronic inflammation and the anterior pillars were slightly injected. The thyroid gland was slightly enlarged. The heart showed a slight systolic murmur at the apex; there was a definite right scoliosis in the lower dorsal and upper lumbar region and marked prominence of the upper lumbar vertebrae. Some resistance and tenderness were found in the lower left quadrant. Note was made of the skin eruption confined to the chin and right cheek. The urine volumes were normal, elimination and balance good. One specimen showed a very slight trace of albumin. The nitrogen partition was normal. The blood showed a slightly low haemoglobin and a slight leucocytosis, the increase occurring in the neutrophilic elements. The blood showed chemically a relatively high uric acid. The serological tests were negative. The phthalein output was normal and the alveolar CO_2 was low. The patient was 5 per cent below her predicted weight and had somewhat less than her calculated lung volume. The basal rate was observed as 15 per cent below prediction, the true rate being probably somewhat lower, as the patient was slightly nervous; earlier and less satisfactory tests had given —6 per cent and —10 per cent, respectively. The pulse was normal and the blood pressure low. An orthopedic examination defined the scoliosis as deriving from faulty posture and of no real significance. A neurological examination failed to find evidence of organic nerve disease and the history was regarded as suggestive of migraine, as both transient palsies and hemianopsia may be associated with this condition. Endermal tests gave only negative response to a large number of food proteins. The patient's sugar tolerance was 50 per cent above prediction. A heart examination gave no evidence of disease and a cardiogram confirmed this opinion. X-ray studies of the sella, skull and sinuses were normal, as were those of the spine, pelvis and hips. The eye examination showed yellowish discs, enlarged blind spots and a possible slight contraction of the form fields. A dermatological examination defined the presenting condition as rosacea.

Discussion: In the evaluation of this case it is essential to remember that the patient has a definite endocrine condition of surgical origin, which inevitably influences certain of the results. For example, the low alveolar carbon dioxide and the low blood pressure should be ascribed to the hypogonad condition. With so relatively slight a drop in the basal rate, even though the true basal were not obtained, one would not normally trace a thyroid influence, certainly not one of a magnitude to produce the definitely increased sugar tolerance which in our experience is only found in profound changes of thyroid activity. The bulk of the evidence was felt to point to a bilobar pituitary failure, and this, with the patient's surgical hypogonadism, defined a pluriglandular condition. Whole pituitary medication was recommended and reports from the referring physician record a marked improvement in the patient's general picture and at the end of three months a practically complete disappearance of the skin eruption.

Case S-1343. The patient's chief complaint, as offered by herself, was a susceptibility to infections of the respiratory tract coupled with asthma. During the past year she has been extremely fatigable and has felt that her resistance was particularly low. She ascribed this to her repiratory difficulty. During the preceding winter she had a heavy cold and a severe, persistent, productive cough. The family history was not significant beyond a record of longevity in the older generations. The patient had been married for 23 years and had borne two children without a miscarriage. Six years before admission the ovaries and uterus had been removed. She stated that she was a delicate child and had never been rugged. The history included a few minor ailments and an appendectomy 20 years before. She had hay-fever every June. She had been treated with serum for her asthmatic attacks with apparently excellent results. The catamenia was established at 14 and the menstrual history was normal up to the time of her pan-hysterectomy. Physical examination showed a fairly developed and well nourished woman in the late forties. The hair was gray and abundant. The tonsils were enlarged and inflamed. The patient stated that she had had bad tonsils for a long time, but had been advised against operation. The chest showed some dulness, scattered rales and somewhat increased focal fremitus. The heart showed a soft systolic murmur, apparently not transmitted. There was a slight mass in the right lower quadrant which the examiner ascribed to adhesions. From the patient's history as given, the appendiceal condition was bad at the time of her operation. The residual examination was not significant, including the routine neurological study. The urine volume was well in excess of two liters, the elimination good, but the balance poor; is otherwise normal. The nitrogen partition showed a low, but adequate, protein intake with a markedly high residual fraction. The blood morphology was substantially normal except for a 14 per cent eosinophilia which was ascribed to the hay-fever and asthmatic condition recorded in the history. The blood uric acid was high. The phthalein test, alveolar CO_2 tension and vital capacity comparisons were all normal. The serological tests were negative. An unsatisfactory basal rate gave a level of —7 per cent. The true rate was certainly lower, although how much it would be impossible to say. The patient declined to repeat the test. She showed a hypertensive blood pressure and a somewhat slow pulse. Radiography showed the sella to be large and recorded a thinning of the wall of the posterior clinoid, presenting a picture suggestive of an hypophyseal tumor. The sinuses were normal, as was the chest. The eye examination showed moderate vascular sclerosis and yellowish discs; the right blind spot was slightly enlarged and there was a suggestion of cutting in the right form field. The patient's sugar tolerance was 100 per cent above prediction.

Discussion: The patient's clinical history determined ovarian failure. Superimposed upon this was an undoubted pituitary involvement. With the marked increase in the sugar tolerance and the presumptively lowered basal rate this latter condition would be a bilobar pituitary failure. The roentgenograms gave some evidence of pituitary tumor. On the basis of this diagnosis the patient falls conventionally into the pluriglandular group.

Case S-1669. The patient's chief complaint was of recurrent temporal headaches. These started in childhood, but with the onset of catamenia they increased in frequency and severity. They had been initially unilateral in onset, but would spread over the whole frontal region in their course, which was usually three to four days. Seventeen years before admission, the patient had one ovary removed, and ten years later the uterus and remaining ovary were ablated. Since this latter event the headaches had been still more exacerbated, might be accompanied by nausea and vomiting, and were associated with pronounced mental depression. In the family history were recorded similar headaches in the father and one sister, but otherwise nothing significant. The patient had had all of the minor ailments of childhood, pleurisy following tonsillitis at 12, and several later attacks of the latter until a tonsillectomy 15 years before. She had had several brief attacks of mild generalized arthritis. She had worn glasses for many years without influencing her complaint. Her appetite had been fair, with the voluntary elimination of sweet and rich foods from her dietary. She was severely constipated and had been troubled for years with hemorrhoids. The catamenia had been established at 12, was at first irregular, but after some two years became regular with somewhat shortened rhythm. The flow was normal in amount. An uneventful menopause had occurred some six months before her hysterectomy, which was for a fibroid tumor.

The physical examination showed a well-developed and nourished woman of 51, with slight pilosity on the upper lip, but other hair distribution normal. The remaining findings were completely normal. The urine volume was ample, the balance of the observations not significant, except for a high residual nitrogen fraction. The blood showed a lymphocytosis and slight (3.5 per cent) eosinophilia. The blood uric acid was relatively and absolutely high, the serological tests were negative, and the phthalein output and CO_2 level normal.

She was at her predicted weight, but appreciably below (36 per cent) her calculated lung volume. A fairly satisfactory basal rate measurement was 12 per cent below prediction, with somewhat lowered pulse and blood pressure. X-ray plates showed a large sella and obstructed nasal fossae, but otherwise normal findings. The sugar tolerance was 100 per cent above her normal level. The eye examination showed yellow discs, enlarged blind spots, and some cutting of the fields, more marked in the left eye.

Discussion: The picture given above defines a bilobar pituitary failure, with but few of the conventional evidences lacking. In addition, there is superimposed a surgical hypogonadism, making the diagnosis technically pluriglandular failure.

GROUP IIIa. THYROID FAILURE AND GONAD FAILURE

CASE S-686. This patient was a girl of 19, who complained of frequent headaches in the frontal and supra-orbital region, from which she had suffered for about a year. A recent eye examination had failed to disclose any cause for this complaint, and she had been referred for an endocrine study. She also complained of a pain in the sacro-iliac region. She became dyspneic on the slightest exertion and was very fatigable. The family history was entirely irrelevant. The patient's own history showed a few minor ailments and a tonsillectomy and adenectomy some two years before. She had been married in the fall of the preceding year and had aborted an early foetus inside of three months. She described her headaches as sharp in character and aggravated by pressure. The face became flushed and there was a general feeling of malaise. The frequency varied from every other day to once a week, and their incidence was apparently not associated with any other event. She had several sore-throats since her tonsillectomy. She complained of intervals during which the nipples become red and sore and were painful. The menses began at the age of 14, were regular, and the periods apparently normal. Physical examination showed a well-developed, somewhat undernourished girl. There was a slight tenderness over the frontal sinus, poor occlusion of teeth and numerous small papules on the areolae of both breasts. The chest and abdomen were normal, and the remaining examination not informative. The urine volume was normal, elimination and balance poor; albumin was recorded, but the sediment was normal. The residual nitrogen was somewhat above the normal. The blood showed a slight but definite secondary anaemia with a slight lymphocytosis. The blood chemistry was normal; the serological tests were negative, the phthalein output somewhat low. The patient was 10 per cent under weight and the lung volume was somewhat below prediction. The basal rate was 29 per cent below the normal, and the pulse, blood pressure and temperature all definitely low. The sugar tolerance was 25 per cent below prediction. Alveolar carbon dioxide was a low normal value. Radiographs of the skull were normal. A pelvic examination disclosed a resistant mass in the region of the right adnexa, which was interpreted as either a cystic ovary or hydrosalpinx. The eye findings were normal.

Discussion: At the time this case was studied it was felt that the urine picture and the basal rate determined a thyroid failure, while the lowered sugar tolerance, coupled with the results of the pelvic examination, were interpreted as indicating some degree of ovarian failure. In the light of later experience it seems doubtful if this case warrants a pluriglandular diagnosis, as the dysfunctional state of the thyroid (transition) would probably account for all of the departures from the normal. In view of the fact, however, that there was tangible disease apparently associated with one ovary, we have felt that in fairness this case should be retained as presenting a possible multiple glandular involvement.

CASE B-109. The patient's presenting complaint was given as indigestion, and the duration of the illness as 18 years, the condition following a bilateral oöphorectomy. The family history gave the death of the parents as from cardio-vascular disease; one of four sisters had hyperthyroidism; and one of five brothers died of hydrocephalus at eighteen months. The patient had been married for over 20 years, had borne one child and had one miscarriage and one ectopic pregnancy. She had had the usual illnesses of childhood, together with diphtheria, broncho-pneumonia 10 years previously, influenza at the time of the epidemic and cystitis several years before. She complained of occasional headaches, vertigo, and fainting spells. These latter she traced to peculiar sensations which would occur in her laparotomy scar. She reported occasional spasms of the epiglottis. She was greatly troubled with nausea and vomiting, which would occur usually an hour after eating. The bowels were constipated; there was some nocturia. The catamenia was established at the age of 16, was always irregular with increased interval and scanty flow until her operation terminated the function. Prior to her hysterectomy, a nephropexy had been performed and 8 years after she was operated upon for lysis of adhesions and had an appendectomy. Physical examination showed a well-developed and somewhat under nourished woman, nervous and garrulous, of about 50 years of age. The hair was thick and soft and that on the body was normally distributed. The teeth showed much dental attention; the thyroid was not enlarged; the lungs and heart substantially normal, and there was some tenderness in the right lower quadrant. The remaining examination was not significant. The urine volume was normal, elimination and balance poor; albumin was recorded, and the sediment showed much epithelial debris, numerous leucocytes and a few blood discs. The residual nitrogen fraction was positively high. The blood showed a marked lymphocytosis. The blood chemistry was normal except for a somewhat high blood sugar which was not verified on subsequent examinations. The serological tests were negative. The phthalein test was normal. The sugar tolerance was normal for one with the patient's gonad deficiency. Alveolar carbon dioxide was definitely low. The patient was 14 per cent under weight and with a somewhat depressed lung volume. The basal rate was —30 per cent, with low blood pressure, slow pulse, and somewhat low body temperature. The urea curve was normal. The eye examination showed slightly enlarged blind spots, but otherwise normal. X-ray plates showed a normal skull and sella, together with normal heart and lungs. A gastrointestinal series of plates was normal. A pelvic examination gave results in accordance with the patient's history. A genitourinary examination defined an existing cystitis. A neurological examination failed to disclose evidence of organic nerve lesion. The patient had had, however, psychotic episodes in the past, was distinctly psycho-neurotic at the time of her examination, and some time after her discharge had an acute psychotic episode.

Discussion: Analysis of the data here demonstrates a thyroid failure superimposed upon the surgical hypogonadism. Naturally, with the patient's stormy surgical history, the bladder condition, and the mental and nervous instability, the picture lacked the clarity of outline of an uncomplicated thyroid failure. Thyroid medication was advised and for a time was followed with marked evidence of clinical improvement. Later contact with the patient has been lacking.

CASE B-599. The patient was a woman of 54 complaining of headaches and of fatigability. The former condition had obtained for the preceding three years, occurred at intervals of approximately four weeks, and lasted from one to three days. The pain started in the left occipital region and usually extended forward to the left parietal or even the left frontal. It also radiated downward to the shoulder and arm. Simultaneously there was pain in both feet in the region of the arches. The rhythmic occurrence of the headache would suggest an association with the menstrual cycle which, however, was denied by the patient's history. The menses had been established at the age of 14, and six years later a pan-hysterectomy was performed. The inference drawn from the history was that this somewhat drastic method was adopted to correct extremely painful and debilitating periods. An interesting statement made by the patient in connection with the headaches was that they were always preceded by a period of "black rage," caused by some trivial event, and that they were always followed by periods of profound exhaustion. The family history was not significant. The history included the minor ailments of childhood, attacks of rheumatic fever at 16, at 20, and at 30, the last of these being followed by an arthritis of several years' duration, but without apparent cardiac complications. There had been several nervous breakdowns during the patient's life. She had had abscessed ears requiring operation. At the age of 7 she was struck on the head by a railroad gate and was rendered unconscious for several hours; again, at 14, trauma to the head caused another period of unconsciousness. Beside her hysterectomy she had had a gall bladder operation 8 years previously and, more recently, a tonsillectomy. She had been over weight for a number of years, a condition only partly controllable by dieting. She stated that she was nervously unstable, easily frightened and tended to be irritable. At the age of 12 she had a severe attack of psoriasis, which lasted for about a year and a half. She apparently had a food sensitivity to eggs. Physical examination showed a somewhat obese woman in the middle fifties. She was moderately deaf, but the remaining findings were practically normal. The urine volumes were normal, elimination was fair, the balance poor and the remaining examination negative. The nitrogen partition was normal. The blood showed a slight secondary anaemia and was definitely lymphoid. The blood chemistry was normal; the serological tests were negative; the phthalein output was normal. The sugar tolerance showed a negative response to 20 grams and a positive response to 30. This would indicate an increased tolerance for one in the patient's gonadal condition. She was 31 per cent overweight and had lost nearly half her predicted lung volume. The urea curve was normal. Alveolar carbon dioxide was at a normal level. Her basal rate was reported as —21 per cent, with low blood pressure, pulse rate, temperature and respiration rate. The patient was outwardly calm, but confessed to a definite nervousness, evidence of which she had concealed. A pelvic examination gave results in harmony with the patient's earlier history. An endermal test showed a negative response to egg albumin. A nose and throat examination showed a slight septal deviation. X-ray examination of the skull showed a slight elevation of both tables, posterior to the junction of the coronal and sagittal sutures; the sella was small and regular; the frontal sinuses were irregular and blurred in outline, a condition consistent with an old sinusitis. The audiogram showed a loss of hearing in both ears, more pronounced in the higher frequencies. The eye examination showed normal fundi, enlarged blind spots, and a marked cutting of the upper form field demonstrably due to drooping lids. The neurological examiner commented on the evidences of an earlier frontal sinusitis and possible fracture of the skull in childhood, but failed to discover any evidence of organic disease.

Discussion: Taking the results produced by the patient's castration, it is obvious that a second possible endocrinopathy is superimposed on the surgical condition. With the increased sugar tolerance and moderate depression of the basal rate, one would instinctively think of a pituitary failure as the underlying functional endocrinopathy. The history of the blow to the head would also turn attention in this direction. Further analysis, however, makes the case for the pituitary much less certain. The physical findings associated with the basal rate determination are of the lower order of thyroid and not that of pituitary failure. Again, the blood shows only a lymphocytosis, there being no increase in the eosinophiles. The blood uric acid was normal. The basal rate was at least 21 per cent below prediction and there was every probability that the true rate fell somewhat below this. The sugar tolerance would seem to offer a stumbling block since there is a definite increase here wholly disproportionate to the magnitude of any probable thyroid failure. This patient was castrated within six years of the establishment of the menstrual function and thirty-four years before the time of study. As one of us has reported elsewhere, opportunity had occurred to study another patient who, like the present one, had been castrated at a very early age and many years before the study was carried out. She, too, showed a sugar tolerance of 30 grams. It seems possible, although the suggestion is offered only tentatively, that with early castration and the subsequent lapse of several decades, some sort of a compensatory process might have come into being. Another possible explanation could be that the thyroid failure was of such a magnitude as to condition an increased tolerance. While the lowering of the basal rate was of very moderate proportions, the value observed was certainly above the truth. Whether this assumption be correct or not, the present patient patently presents an endocrine disorder superimposed upon her surgical hypogonadism. The thyroid seemed to us more probably at fault, and the opinion was offered on that basis. The controlled use of thyroid medication was recommended.

Case B-662. This patient came for study complaining of overweight, although she was 8 per cent below prediction. Subsequent knowledge of this fact by the patient did not influence her earlier conviction. She also reported herself as markedly fatigable and she complained of a swelling of the hands and wrists. She dated all of her complaints from the birth of her only child, an event that had taken place some 11 years before. She was delivered by Cæsarean section and at this time a pan-hysterectomy was performed. Within a few weeks of her operation she was obliged to take a long and fatiguing journey, and shortly after this her hair began to fall out. Under treatment this condition was corrected. Prior to her successful pregnancy the patient had frequently conceived, but had uniformly induced abortion, the total number of which she had forgotten. The family history included cardiac disease in both parents, tuberculosis in a surviving brother and several other brothers who died in early infancy. In her own history, she reported minor ailments in childhood; a very severe case of influenza during the War, which she was told left her with an impaired heart, and a record of several nervous breakdowns. For a short time in the previous year she had suffered intermittently from precordial pain, but had had no attacks recently. She stated that she had a large appetite and, in the main, a perfectly functioning alimentary tract. Under the stress of nervous excitement, however, she had a tendency to vomit. She established the menses at the age of 11, and the function continued normal and regular until her castration. Physical examination showed a well-developed woman in the earlier forties. The hair was somewhat scanty, that on the body showing a normal distribution. Percussion demonstrated a possible cardiac enlargement; the blood pressure was definitely low. There was tenderness in both lower quadrants of the abdomen and some question of the tendon reflexes. The urine volume was normal, elimination fair, balance poor; albumin was recorded, but the sediments were normal. Her protein intake was below a maintenance level; the nitrogen partition formula was substantially normal. The blood showed a slight secondary anaemia, a distinct lympocytosis, and a slight eosinophilia. The nitrogenous constituents of the blood were all slightly above normal, the uric acid showing the smallest relative increase. The serological tests were negative. The phthalein output was below normal, the sugar tolerance normal. She was 8 per cent underweight, with a substantially normal sitting height index. The lung capacity was unimpaired. The urea curve showed fair elimination. The basal rate was —25 per cent, with marked depression of the blood pressure and temperature and a somewhat slow pulse. A heart examination gave no evidence of organic disease nor did the cardiogram, failing to confirm the earlier reports. In the examiner's opinion her cardiac symptoms were of functional nervous origin. The neurological findings were normal, failing to confirm the findings earlier reported. A pelvic examination yielded results in accordance with the patient's history. The eye examination showed some vascular sclerosis and otherwise normal findings.

Discussion: The patient was a markedly neurotic individual, presenting in a striking degree the insistent egocentricity of the gonad failure. She was wholly incooperative, a fact which influenced some of the tests and precluded the securing of others. She was wholly disingenuous in regard to her history; such statements as we have recorded above are, so far as we know, fairly accurate. There was no question that there was a surgical hypogonadism. Superimposed upon this was a second endocrine defect. With the level of her basal rate, with the normal sugar tolerance, the evidences of lowered kidney permeability, the normal eye findings, to name but a few, the thyroid seemed to be the most probable focus of failure. Thyroid medication was advised. This case falls technically into the group of pluriglandular syndromes. Its multiple character, however, derives from the surgical operation.

CASE B-976. This case presents unusual points of interest, as it gives the details of the study of a male castrate with a second superimposed endocrine defect. The patient was a man 67 years of age who gave as his chief complaint a sexual disorder. The history showed that 35 years previously (November, 1892) he had had a fall from a bicycle and struck his head and was rendered unconscious for several hours. He had a few days of convalescence and then returned to work, apparently none the worse for the experience. Six months later he began to be troubled by indigestion associated with nervous exhaustion and occasional fainting spells. At about this time he found that sexual intercourse had become distasteful and was followed by a dull headache. In a very short time he lost all sense of desire. He was placed under treatment and began to improve. With his improvement sexual desire returned, but there was premature ejaculation, and this disturbed him greatly. He had been married some two years before his accident and his wife had borne one child, a daughter. The unsatisfactory character of his marital relationship gave rise to a marked emotional instability that seemed to amount to a psychoneurotic condition consisting mainly of a phobia of sexual intimacy. Two years after the accident he had a small hydrocele, and this was corrected with removal of the testicle. A year later he was advised to have the other testicle removed to correct the mental condition, and in the face of opposition by a consulting physician complete castration was performed. This second event was in 1898, or 30 years before his admission for this study. Between 1898 and 1901, rest and treatment by a neurologist gradually brought about some improvement. As a result, he was able to resume work and to reestablish his financial independence. This later condition obtained from 1901 to 1914; there was some continued improvement, and the occasional severity of the nervous instability did not prevent employment. Again, two years later, he developed urinary symptoms and cystoscopy demonstrated a stricture. Dilatation with sounds produced some betterment. A year later the veramontanum was removed. Following this operation he had a phlebitis in the left leg. In spite of his gonad defect, for a number of years close association with women had produced marked reactions which he called sexual disturbances. During this interval he had been aided somewhat by psychoanalysis and in 1923 a course of steam baths brought temporary relief. A course of treatment with orchic material was followed by a recurrence of the earlier symptoms and led to a discontinuance of the therapy. Subsequent to this he was given a brief course of thyroid therapy which, as it was based on basal rates which were always reported as within the normal range, never exceeded a dosage of more than one grain a day. This treatment yielded no result, and two years prior to admission to this Clinic the patient had come under the control of a clinical psychologist who had produced very marked improvement in the neurological and mental picture. As there were obviously physical difficulties as well, our study was undertaken to ascertain the patient's functional level. It should be mentioned in passing that the reason given for the second orchidectomy was to eliminate pain in the pudic nerve. The family history showed a rather remarkable longevity in his immediate relatives and one case of epilepsy in a brother. As noted above, he had been married and his wife had borne one child prior to his mutilation. He reported relatively few ailments outside of those recorded above. "Inflammation of the bowels" at 16, mild diphtheria at 20. and several traumatic injuries to the extremities were reported. He complained of head pains starting in the occiput and radiating forward, but not of true headaches. There had been some loss of hearing in the left ear. His teeth had always been poor, and while under his endocrine medication he had periods of "nerve aching" in the jaws. During his long illness there had been brief periods when he was slightly jaundiced, and he complained of more or less gastro-intestinal disturbance for the preceding four decades. He recorded tenderness along the course of the sciatic nerve, also tenderness on both sides of the lumbo-sacral spine.

Throughout his illness he stated that he had been very nervous and irritable and was introspective, readily excited and emotional. The psychologist found a history of anxiety neurosis, but there was no hallucinations or delusions. He had been markedly fatigable for many years. Physical examination showed a well-developed and nourished man with a tendency toward obesity in the abdomen and chest wall. The protuberant abdomen determined a poor posture, increasing the lumbar lordosis. The hair on the vertex was steel gray and moderate in amount. The pupils showed a sluggish light reaction and a beginning arcus senilis was noted. There was apparently a bilateral deafness. The teeth were in fair condition, the tonsils apparently not offending. The heart, lungs, and abdomen were normal. The penis was short and small, the scrotum small and empty. The sparse pubic hair was of female distribution. In addition to the lordosis noted above, there was a moderate right lumbar scoliosis, a tenderness on palpation at the levels of the seventh thoracic and about the lumbosacral joint; also some tenderness on pressure in the right portion and along the courses of the sciatic nerves. The cranial nerves were intact. The normal reflexes were active. The train and content of thought were normal, and the routine neurological findings otherwise normal. The urine volume was normal, elimination fair, balance good. Albumin was recorded in both specimens. The nitrogen partition showed a somewhat high residual fraction. The blood showed a slight but definite secondary anaemia. There was a relative increase in the endothelial leucocytes and a slight relative increase in the eosinophiles. The nitrogenous constituents of the blood were all slightly above the normal. The serological tests were negative. The phthalein was definitely low. Galactose tolerance was somewhat depressed. He was recorded as 14 per cent overweight, but was actually in excess of this, as the sitting height index was high. There was a perceptable loss of lung volume. Alveolar CO_2 was at a normal level. An urea index was a low normal value. The basal rate was 30 per cent below predicition, with bradycardia, sub-normal temperature, and low blood pressure. A genitourinary report indicated normal conditions. Repeated examination of the patient's stools showed no parasites, ova or blood. An ear examination gave normal findings. The audiogram showed loss of hearing, which was more pronounced in the upper register. The Barany test findings were normal. The blood fragility was normal. A neurological examination gave no evidence of organic disease. A cardiogram was substantially normal. The eye examination showed normal pupillary reaction, yellowish discs, some vascular sclerosis, and a cutting of the upper form field, due to drooping lids. An orthopedic examination confirmed the existence of a low backstrain. Radiography showed a proliferating arthritis of the right astragulo-scaphoid articulation; the right sacro-iliac joint picture was hazy and indistinct, and there were asymmetrical articulations in the 4th and 5th lumbar region. There were hypertrophic spurs on the dorsum of the right foot. The skull, sinuses, and sella were normal. The teeth were not diseased. A gastro-intestinal examination gave normal findings. A Graham test by the intravenous route was also normal. The patient had a slight skin eruption on the lower left leg which was defined in a dermatological examination as a mild erythematous eczema. The icteric index and Van den Bergh tests gave normal findings, but an examination of the duodenal contents by the McClure technique showed a marked liver dysfunction. A very full statement of the mental aspects was made available through the courtesy of the referring psychologist. It does not lend itself, however, to presentation in abstract form.

Discussion: Experience with other male castrates has demonstrated that the condition produces but minor changes in the level of vital function tests. With due recognition of this fact, the picture presented by this examination shows a clear-cut thyroid failure of considerable magnitude and probably of long duration. The demonstrated liver dysfunction explains the somewhat lowered sugar tolerance. Apparently this difficulty was confined to the liver and did not include the gall bladder. An interesting feature in this case is the failure of the lowered thyroid activity to produce a lowered sexual level. That his sexual abnormality, however, was confined to the mental reactions and secondary sexual emotions and was probably engendered in part, at least, by psychogenic factors, explains in some measure the presenting anomaly. In our experience, male castrates are relatively rare, at least those who are willing to undergo investigation. We feel particularly fortunate in the opportunity to have studied this case, which conventionally falls in the pluriglandular group.

CASE S-1843. The patient's chief complaint was of ready fatigability, coupled with pain over the sternum and radiating to the left shoulder. She was also extremely nervous. The patient was 48 years of age at the time of the study and had matured at the age of 17. The periods were very irregular, with both increase and diminution in the interval. The flow was profuse. Three years and a half before admission she flowed steadily for a period of six months. Operation was recommended and the ovaries and uterus removed. Up to that time the patient's health had been good. Her present difficulties, she felt, dated from the operation. Within the preceding six months the pain and a numbness of the fingers of the left hand had developed. The family history included that of the mother's death of cancer, the father's from gangrene. The patient had been married 30 years, had always desired children, but had never conceived. She reported only minor ailments, pneumonia at the age of 5, and a nasal operation many years before. Fifteen years previously she had been struck by an automobile, and although she sustained no fractures, was placed in a jacket for a few months; she had shown no symptoms subsequently. Some six years before she began to have severe headaches, but these disappeared after her operation. For a number of years there had been a gradual loss of hair and slow, progressive impairment of vision. For the past few years she had had occasional attacks of dyspnoea. She had a tendency to constipation and stated that she found it necessary to remove the feces manually. Her physical examination showed fair development and nourishment, some thinning of the hair on the vertex, and body hair normally distributed. The eyes were normal. The tonsils were open to suspicion. There was no thyroid enlargement. Heart, lungs and abdomen were normal. The skin was dry and atrophic and there was some hypertrichosis on the upper lip and chin. The routine neurological findings were normal. The urine was scanty, the elimination and balance poor. The nitrogen output indicated an inadequate protein intake; the partition formula was substantially normal. The blood showed a lymphocytosis and a slightly high value for the nitrogenous constituents; the serological tests gave normal findings. The 'phthalein output was below normal; alveolar CO_2 at a normal level. She was recorded as 4 per cent below her predicted weight, with a significant loss in predicted lung volume. The basal rate was —24 per cent. The sugar tolerance was normal for her castrate condition. The pulse and temperature were distinctly low. The blood pressure showed an upward tendency, although falling far short of a hypertensive level. A nose and throat examination showed a minor septum deviation and unoffending tonsils clearing the earlier finding. A cardiogram confirmed the bradycardia and was otherwise negative. The eye examination showed poor convergence accommodation, marked cutting of the upper form fields from lid droop, and slightly enlarged blind spots.

Discussion: In addition to the surgical hypogonadism, the patient had a fairly typical thyroid failure, without myxedema, which was probably of long standing. Technically, the case is pluriglandular. It would be interesting to speculate on what would have been the influence of thyroid medication on the excessive menstrual flow which led to the patient's castration.

GROUP III-b. THYROID DYSFUNCTION AND GONAD FAILURE

CASE S-179. The patient's chief complaint was of weakness and dyspnoea. The condition followed operations in two stages for the partial removal of a hyperactive thyroid. After the second operation the patient had gradually become fatigable and developed a lack of strength. She had been much underweight as a result of the earlier toxic thyroid and had gained 40 pounds in the interval. During the past two years she had been greatly troubled with hot flashes and had noted coincidentally a marked diminution in the menstrual function. Previous menstrual history showed maturity at 12 and a regular rhythm with somewhat excessive flow. She had been married 17 years and had borne two children without miscarriage. Her family history was not relevant. The patient had had minor ailments, together with scarlet fever at 16, typhoid at 18, the two thyroid operations already noted, a ventral suspension of the uterus, and two repair operations on the vagina. She stated that her teeth were very sensitive and required constant care. The year before she had had a brief attack of indigestion. The bowels were regular. Recently she had developed a slight vulval pruritus. Physical examination showed good development and nourishment. The patient was somewhat slow in her physical and mental response. The skin was moist, the hair normal in amount and distribution. There was no residual thyroid enlargement. The heart, lungs, and abdomen were normal, as were the structures considered in a routine neurological examination. The urine volume was normal, elimination and balance poor; the findings were otherwise normal. The nitrogen partition examination showed an inadequate protein intake and a normal formula. The blood showed a slight leucocytosis, with increase in the neutrophilic elements. The blood was normal chemically. The serological tests were negative. The 'phthalein output was somewhat below normal; alveolar carbon dioxide was definitely low. The patient's observed weight corresponded with prediction. There was some lessening of the lung capacity. The basal rate was reported as —11 per cent, with a slightly rapid pulse, a slightly febrile temperature, and a very low blood pressure. Radiography of the skull, sella and chest showed all these structures to be normal.

Discussion: It is a question in our minds whether this case properly belongs in the pluriglandular group. There is patently a thyroid dysfunction dating from the earlier overactivity. The history of the recent pruritus suggests a possible glycosuria, although the specimen of urine examined was sugar free. The blood pressure was very low. The alveolar carbon dioxide was below the normal. Additional opportunity for observation was requested on this patient, but could not be secured. While we do not regard the case as clearly belonging to the pluriglandular group, we feel that there are enough evidences to warrant the suggestion of a gonad failure superimposed upon the thyroid condition.

CASE S-230. This patient offered an interesting study, as both of her two endocrinopathies existing at the time of study had surgical backgrounds. Sixteen years before admission the patient noted a glandular enlargement in the neck. Medical consultation defined a cardiac insufficiency, and the patient was hospitalized for rest. During her stay in the hospital she was given tuberculin for the glandular condition. This treatment produced no result, and subsequent x-ray treatment was ineffective. Three years before her admission to this Clinic the neck condition was diagnosed as a goiter and a portion of the gland removed. At about the same time she was also operated upon for a uterine fibroid and a bilateral ovariectomy was also performed. Prior to the removal of the thyroid the patient experienced no symptoms which she felt could be referred to the condition. The family history was negative. The patient had had the usual childhood diseases, and rheumatic fever 35 years before. The menstrual history was entirely normal up to the time of her laparotomy. Her remaining history was entirely negative. The physical examination showed a well-developed and somewhat obese woman of 48. Beyond the scars of her two operations the only point of significance lay in a systolic murmur at the apex of the heart which was transmitted to the axilla. There was apparently an aortic insufficiency and regurgitation. The urine volume was scanty; elimination and balance were poor. The urine contained less than a gram of sugar and was otherwise normal. The blood was markedly lymphoid, and there was a slight secondary anaemia. The blood was normal, chemically. The serological tests were negative. The 'phthalein output was normal. Her alveolar CO_2 was of normal value. The patient was 20 per cent overweight and about 30 per cent below her predicted lung volume. A fairly satisfactory basal rate was 6 per cent below prediction, with a somewhat low blood pressure, normal pulse and temperature.

Discussion: There can be no question in this case as to a lowered gonad activity, but the level of the thyroid function cannot be so simply resolved. It would seem probable that the lowering of the basal rate produced by castration was compensated by a residual slight hyperactivity of the thyroid. The lowered sugar tolerance was referable to the gonad condition. Its principal interest, in our opinion, lies in the slight departures from the normal produced by two multilating operations which produced a condition in which there was a very definite degree of mutual compensation.

CASE S-988. The patient's chief complaint was of intense nervousness and fear, coupled with difficulty in breathing, excessive perspiration, and palpitation. She had a very marked thyroid enlargement and was somewhat obese. The mother had a goiter which began at the age of 25, and when the patient was 23 (26 years ago) she noted that her own thyroid was beginning to enlarge. It grew slowly for a number of years, then remained stationary for a still longer interval, but had begun to grow again in the preceding three years. With this second growth period the majority of her symptoms had developed. The choking sensation in her throat was one of her principal difficulties. She had been obese for a number of years. Some 10 years before both ovaries had been removed and her obesity apparently began after this operation. The family history, outside that of the mother, showed only diabetes in an uncle. The patient had been married for 20 years and had borne two children without miscarriage. The additional records showed only minor ailments, recurrent sore-throats, an occasional dull headache, and some loss of vision. She believed that the eyeballs had protruded slightly during the last few years. A tonsil and adenoid operation a number of years ago had diminished but not eliminated her tendency to sore-throat. The gastro-intestinal history was not suggestive. The menses were established at 15 and were always irregular with an erratic rhythm. Physical examination showed a moderate obesity. There was some difficulty in breathing, a slight suggestion of exophthalmos, hypertrichosis on the lip and chin, excessive pilosity on the limbs, but female distribution of pubic hair. There was marked thyroid enlargement and forward or backward movement of the head produced difficulty in breathing. The heart and lungs were normal. There was an ill-defined tenderness in the abdomen on deep pressure. The extended fingers showed a fine tremor. The urine volume was slightly low; elimination and balance were poor. Albumin was recorded; the findings were otherwise normal. The protein intake was ample; the residual nitrogen fraction much above the normal. The blood showed a slight secondary anaemia and a 66 per cent lymphocytosis. The blood analysis showed slight increase in all of the nitrogenous constituents. The serological findings were normal. The phthalein output was low, and the alveolar carbon dioxide, normal. The patient was 36 per cent above her predicted weight and 40 per cent below her predicted lung volume. The basal rate was —13 per cent, with a somewhat rapid pulse and lowered blood pressure. Radiography showed a normal sella and normal mediastinal shadow. An examination of the mouth showed many dubious teeth, heavily crowned. A nose and throat examination showed hypertrophied, infected tonsils and a non-obstructing septum deviation. A neurological examination disclosed no abnormalities. The eye findings were practically normal. Her sugar tolerance was depressed slightly below the level conditioned by her castration. A repetition of the basal rate a few weeks later gave a level of —1 per cent, with a somewhat more rapid pulse.

Discussion: The patient's surgical hypogonadism determines one factor in her pluriglandular definition. She also had a definite thyroid enlargement which we were inclined to believe was in a dysfunctional state. If the thyroid were slightly overactive it would exercise a compensating influence in the lowering effect of the castration. It would also account for her lowered sugar tolerance, as has been noted at length in an earlier thyroid paper. While again the case is not clear cut, the bulk of evidence pointed to a thyroid dysfunction superimposed upon a surgical hypogonadism. Both were of long standing. The patient was not regarded as a suitable subject for operation at the time, but was advised to remain under observation in anticipation of a change in the level of thyroid activity. Iodine medication was suggested. A year later the patient returned for a repeated study and showed almost identically the same picture as that first presented. The significant changes were a loss of some 13 kilograms in weight, an increase in the evidences of kidney impairment, and a definite increase in the thyroid size. In spite of these disadvantages, the patient reported herself as feeling very much better, except for increased difficulty in breathing. There was no change in the relative basal rate. Operation was recommended with a view to correcting mechanical interference with breathing, and a large tumor mass was removed which was reported by the pathological laboratory staff to be a colloid goiter. The patient is to return for further study in the near future.

CASE S-1023. The patient's chief complaint was of deafness, coupled with flatulency, vomiting and gastric discomfort without pain. This condition had developed some 10 years before admission, at the time of her marriage at the age of 29. The condition was progressive for some 5 years, and 3 years ago an operation was performed for lysis of adhesions. No immediate improvement was manifested, but after a few months she improved definitely and the vomiting became very infrequent. Eighteen months before, however, she began to vomit once or twice a week, gradually increasing in frequency to three or four times a week. On one occasion the vomitus contained fresh blood. More recently, intermittent pain in the right hypochondrium had developed and also in the right lower quadrant. The bowels showed alternating periods of constipation and diarrhoea. The family history was entirely normal. The patient had been married for 10 years without pregnancy. Subsequent questioning developed the fact that she had had both ovaries removed 24 years before, at the age of 15. We could not ascertain the reason for this operation. She offered the usual history of minor ailments, an appendectomy at the time of her ovariectomy, and influenza during the epidemic. She complained of an occasional headache. Her deafness was of about 13 years duration, had been progressive and accompanied by tinnitus, vertigo, and paracusis. The history, while not clear cut, offered some evidence of an earlier otitis. She was subject to head colds, had a nasal obstruction, had had a pyelitis in the previous eighteen months; this had yielded to treatment. The catamenia had been established at 11, and was regular and scanty up to the time of her artificial menopause. Physical examination showed fair development and nourishment. The hair on the vertex was thin and coarse; there was no marked hypertrichosis. The aural acuity was distinctly impaired. The thyroid was not enlarged. The heart, lungs, and abdomen were substantially normal. There was a minor cervical adenopathy, some tenderness in the mid-dorsal region of the spine, and normal routine neurological findings. The urine volume was normal; elimination and balance, poor. Albumin was reported. The nitrogen partition was normal. The haemoglobin was low, the blood cells normal in relative numbers. The blood showed high uric acid, which was not confirmed by later examinations. The 'phthalein, CO_2, and vital capacity measurements were substantially normal. The serological findings were normal. An unsatisfactory basal examination showed —14 per cent, with rapid pulse, a slightly febrile temperature and a downward tendency to the blood pressure. Eye examination showed enlarged blind spots and a slight contraction of the color fields. The audiogram showed marked loss of hearing in both ears. The patient's sugar tolerance coincided with the level produced by castration. A radiographic series of gastro-intestinal plates was normal.

Discussion: This case presented several points of obscurity. When the patient was first seen the lowered sugar tolerance, the high blood uric acid (subsequently found to be in error), and certain points in the history suggested a possible pituitary condition. Additional observations were requested in the course of these, and as the result of questioning, the patient told of her castration at the age of 15. As stated above, we could not learn the cause of this operation, but the fact that it had taken place naturally influenced the interpretation of the findings. Some additional measurements were secured, although not all that were requested. The patient had a definitely low basal rate, although we could not ascertain its real magnitude. It was felt that there was some evidence for the existence of a possible thyroid dysfunction complicating the surgical hypogonadism. The patient was not entirely cooperative, and it has been impossible to verify the tentative conclusion. The case is offered as one of a somewhat doubtful pluriglandularity in which gonad failure is established and the thyroid disturbance a matter of possibility.

Case S-1069. The patient's chief complaints were of a general fatigability, palpitation, and arthritis. Four years before admission she developed an acute attack of arthritis, localized in the left hand and complicated with a cystitis. Under treatment both conditions cleared up in about six weeks. Following these, her fatigability developed. There had been an earlier history of arthritis, somewhat obscure in definition, and generalized as to distribution. The patient had been troubled with sore-throats, but these had yielded largely to a tonsillectomy 2 years before. For several years the teeth had also been a cause of difficulty and a year previously three had been removed, all of which showed abscessed roots. She had had palpitation for the past three years and occasional attacks of precordial pain during the last year. The family history was not especially significant. The patient had been married for 20 years and had borne two children without miscarriage. In addition to the minor childhood complains, she had had small-pox when three months of age. Her surgical history included a repair operation, the removal of one cystic ovary, and, later, a complete castration, an appendectomy, and two tonsillectomies. She had been subject to headaches, but these had been helped somewhat by glasses. There was some loss of hearing in the left ear, and some obstruction of breathing on the left side. She experienced considerable vascular disturbance after the removal of her second ovary. She was constipated and had worn a brace for 15 years for gastroptosis. The menstrual history was not remarkable. She complained of trouble with the sacro-iliac joint for the past 16 years. Her physical examination showed good development and nourishment and substantially normal conditions throughout. The urine volume was normal, elimination and balance poor; albumin was recorded. There was a high residual nitrogen fraction. The blood showed a low haemoglobin and marked lymphocytosis Her non-protein and urea nitrogen were high and uric acid was normal. The serological findings were normal. The phthalein output was normal; alveolar carbon dioxide presented a normal level. The patient's observed and predicted weight agreed; there was some loss of lung volume. Earlier basal rates had shown definitely depressed values. The patient had been under intermittent thyroid medication and at the time of this test a not satisfactory observation was 12 per cent below prediction. The patient was both restless and nervous and the true basal rate was undoubtedly much lower. The blood pressure was low, the pulse normal, but the earlier records had shown a definite bradycardia. Her cardiogram was normal, as was a radiogram of the teeth; the audiogram showed some loss of hearing in both ears, most marked in the lower register; the eye findings were normal. The patient's sugar tolerance was midway between the normal and castrated level.

Discussion: The findings in this case were not entirely clear cut, as there was not full cooperation and the history of the earlier thyroid medication not entirely complete. That the patient had a surgical hypogonadism was established. Superimposed upon this there seemed to be an unquestioned thyroid failure of some degree of severity. As a thyroid failure may raise the sugar tolerance slightly, it was felt that the patient's value reflected the composite influence of both thyroid dysfunction and of the missing ovaries. We have learned indirectly that consistent thyroid medication has produced some betterment.

GROUP IV. THYROID DYSFUNCTION WITH HYPOGONADISM AND POSSIBLE PITUITARY DYSFUNCTION

CASE B-164. That this case is one of a pluriglandular involvement admits of no doubt. The degree and extent of such involvement, however, is in part uncertain. We hold no brief for the accuracy of the complete diagnosis. The patient when first seen was a woman of 40, complaining of nervousness, dyspnoea, choking sensations in the throat, headache, palpitation, loss of hair and occasional swelling in the left leg. Her difficulties apparently began some four years previously, when she became dyspnoeic following what she described as a "heat stroke." It was noted that she had been markedly fatigable prior to this. During her convalescence from the "heat stroke" she was hospitalized and a systolic blood pressure of 240 recorded. On her discharge she visited another hospital, where a diagnosis of thyrotoxicosis was made. A series of metabolism tests gave basal rates varying from +23 per cent to +8 per cent, the majority of them being well within the normal range. Operation followed the diagnosis and the left portion of the thyroid was removed. Prior to the operation the left leg had become sensitive to touch, and there was a burning sensation in it. All of her symptoms improved greatly after the operation, but in a few months they all returned with increased severity. A physician whom she consulted suggested further manipulation of the thyroid function by x-rays, but her previous surgeon advised strongly against any further thyroid interference. Her symptoms increased in severity and she consulted a new practitioner, who informed her that she had a cystic ovary, which he removed, at the same time ligating the thyroid artery. During this period (2 years) the patient was having very profuse menstrual periods at two months' intervals. Following her ovariectomy and thyroid ligation, she had regular periods for four months and then irregularity set in, with increased interval and very profuse flow. During her periods the thyroid region became swollen and a transitory skin eruption developed. She had diarrhoea also at these times. Her last operation left her in a worse condition than previously, and she was ultimately referred to this Clinic for study. With one ovary removed, a portion of the thyroid ablated and the thyroid artery ligated, she presented an interesting endocrine study. The family history was wholly irrelevant. The patient had the common childhood ailments and chronic intestinal disturbance from 17 to 30, which terminated in an intestinal obstruction, for which she was operated upon, with the removal of the appendix. She did not know if anything else were done at this time. The intestinal symptoms cleared up within a year of this operation. She had had a tonsillectomy and adenectomy 9 years before. During the thirteen years of her intestinal trouble she suffered from severe headaches. There was temporary relief after the operation, but they had returned with increasing intensity during the past few years. For many years the patient had been subject to severe epistaxis, her teeth had always been poor and soft, she had a palpitation all her life, and was highly susceptible to respiratory infections. She had a tendency to constipation. The menses started at 14, the history of the interval having been given above. She had hay-fever every August. She had become considerably overweight, the excess being confined to the abdomen and hips. Physical examination showed a restless, poorly developed woman less than 4 ft. 11 in. tall and with a pronounced localized girdle obesity. The hair on the vertex was thin, the mouth showed an anatomical peculiarity with bilateral ridges under the tongue. There was a tenderness on deep palpation in the left lower quadrant. The left leg showed an enlarged calf with a hardened area, which the patient stated was associated with a venous thrombosis. She also stated that there had been a similar condition in the right leg. The remaining findings were normal. The urine volume was slightly high, elimination and balance good. All specimens showed albumin and, one, fine granular casts. The nitrogen partition was normal. The blood showed a slight lymphocytosis. There was no eosinophilia. Non-protein and urea nitrogen of the blood were above the normal level and the blood uric acid was 6 mgm., a value markedly above the normal. The serological tests gave no evidence of lues. The phthalein output was at the low borderline of the normal. The sugar tolerance was greatly depressed, the patient reacting positively with 10 grams, although no glycosuria had been recorded. The sitting height index was above 0.55. The patient was recorded as 22 per cent above prediction and actually was still more overweight. The lung capacity was 30 per cent below prediction. A urea curve showed a normal elimination. Alveolar carbon dioxide was below the normal. The patient's basal rate was within one or two per cent of prediction, but the recorded value was certainly somewhat high, as the patient was nervous. There were several tests, however, made independently, which were highly concordant. The pulse rate was somewhat rapid, the blood pressure showed the hypertensive level 190/110. The pelvic examination failed to demonstrate the adnexa. Radiographic findings of the skull, sella and sinuses were normal. There was no evidence of sub-sternal thyroid, and the heart and lungs were normal. The eye examination showed yellowish discs, enlarged blind spots, and a cutting of the form fields, more pronounced in the left eye and on the temporal side.

Discussion: This patient was seen a number of years ago, at a time when many of the more informative special examinations were not available. To summarize the endocrine status, she was a victim of partial, if not complete, gonad failure. Secondly, there was an earlier history of thyrotoxicosis which lacked support in the recorded basal tests, for which she had had both a partial removal of the gland and a ligation. That this might induce some degree of thyroid dysfunction would seem reasonable. A gonad operation would lower the basal rate somewhat. A compensatory residual hyperactivity of her thyroid remnant would raise it, but as it had brought it only to a normal level this thyroid influence could not have been a very marked one. The gonad failure could drop the sugar tolerance to 20 grams. A thyroid overactivity, to produce a further lowering, would probably be of considerable proportions, much more, at least, than those suggested by the basal rate. The patient was under 5 feet tall, she had a marked girdle obesity, an ample urine elimination, a very high blood uric acid, the significance of which is somewhat lessened by the slight increase recorded in the other nitrogen constituents of the blood; a lymphoid type of blood, a normal nitrogen partition, and low alveolar carbon dioxide, referable, presumably, to her gonad condition. On the basis of all these facts one could conceive of a pituitary disease which had dated back to childhood. That she had a normal sella has no bearing on the matter, since many severe pituitary cases exhibit this condition. We are frankly in doubt as to the complete endocrine status of this case. Surgery has established the thyroid and in part the gonad condition; an initial and participating pituitary condition remains a matter of surmise. Our experience has led us to be very loath to place undue weight upon external appearances, but such observations as those of the eye examination and certain of the laboratory tests can be related to her known endocrinopathies with the greatest difficulty, if at all. With one ovary gone and the other possibly diseased, with a thyroid presumptively in a dysfunctional state, there still remain a group of objective findings that suggest even though they fail to define pituitary involvement.

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The following three papers were published in Volume 13 of ENDOCRINOLOGY. At the beginning of this volume a change in page size was made, necessitating the resetting of these three papers. This resetting has destroyed the original pagination in place of which we have treated each paper as a unit, beginning the paging of each with 1.

Complete reference to the original publication will be found at the close of each paper.

STUDIES OF THE ENDOCRINE GLANDS

VII. AN ANALYSIS OF FIVE HUNDRED CASES SIMULATING ENDOCRINE DISORDERS

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PART I.

In a series of previous communications an objective method for the diagnosis of endocrine disorders has been outlined (1) and a group of clinical studies reported in which it has been applied (2).

In the large number of patients presenting outward evidence of possible endocrine disease (the present group is drawn from a series of over two thousand cases) it is not surprising that a due proportion of them on thorough examination should disclose a non-endocrine etiology. As our studies are concerned with the accurate differential diagnosis of the several endocrine morbidities, such cases form an intrinsic part of any general discussion. From our point of view they are primary in importance, as the basic principle of the diagnostic method is the proven elimination of all possible non-endocrine causes of an observed given result before it may be adduced to support an endocrine diagnosis. The present communication, therefore, deals with the findings from a number of non-endocrine conditions which either present stigmata offering seeming clinical evidence of the recognized endocrine disorders or duplicate the results of individual tests usually associated with some endocrine malfunction. An illustration of the first could be an obesity deriving from gluttony or an amenorrhea of cardiac or renal origin; of the second, the high basal rate associated with leukemia or the persistent glycosuria deriving from syphilis or a lesion of the central nervous system.

Further, speculative endocrinology has, from time to time, deduced from a single symptom a complicity of one or more ductless glands in a condition of known primary non-endocrine etiology. Objective analysis will confirm or deny the warrant of such inclusion and thus define criteria for treatment which are beneficial in both a positive and a negative sense. The indiscriminate use of powerful glandular extracts has nothing to recommend it as a practice, while the results of an uncritical polypharmacy may be disastrous.

TABLE I

Etiological Classification

Group	Pathological Condition Detail	Primary	Cases Secondary	Total	Group Prim. Totals
	Normal Controls	18	—	18	18
Infections	Tuberculosis	19	7	26	56
	Atrophic Rhinitis	4	—	4	
	Arthritis	18	6	24	
	Gall Bladder Infections	10	3	13	
	Primary Focal Infections	5	20	25	
Psycho-Neurotic States	Neuroses	21	1	22	60
	Psycho-Neuroses	24	9	33	
	Psychoses	15	1	16	
Disorders of the Central Nervous System	Primary Lesions of the Central Nervous System	47	3	50	82
	Epilepsy	9	1	10	
	Paralysis Agitans and Parkinson Syndrome	11	—	11	
	Mental Arrest	3	5	8	
	Miscellaneous Nerve Diseases	12	1	13	
Disorders of Metabolism	Malnutrition	14	16	30	35
	Obesity	12	5	17	
	Gout	2	—	2	
	Miscellaneous Bone Diseases	7	3	10	
Disorders of the Cardio-Vascular System	Diseases of Heart	7	2	9	61
	Diseases of Kidneys	22	31	53	
	Cardio-Renal Disease	32	9	41	
Diseases of the Blood	Primary Anaemia	8	—	8	17
	Secondary Anaemia	2	2	4	
	Leukaemias (myel. and lym.)	6	—	6	
	Haemophilia	1	—	1	
Tumors	Tumors, Malignant	6	—	6	20
	Tumors, Benign	6	4	10	
	Goiter, Non-Toxic (1)	8	—	8	
Miscellaneous Diseases	Syphilis (acquired and congenital)	43	14	57	43
	Diseases of the Eye	5	9	14	5
	Diseases of the Ear	57	8	65	57
	Diseases of the Skin	17	6	23	17
	Diseases of Gastro-Intestinal Tract	10	5	15	10
	Diseases of Pelvis	6	4	10	6
	Asthma	11	1	12	11
	Intoxications	2	4	6	2
	Total	500	180	680	500

For these several reasons, the cases presented in the series cover a wide range of disease conditions. Information concerning the general metabolism of some of these is a by-product of the primary investigation and will be discussed at another time. Not frequently, in addition to the primary morbidity, a secondary condition would be apprehensible, of sufficient importance to warrant its inclusion in the general disease picture. These could be concomitant or resultant, but in either case they produce symptoms which constitute a integral part of the general condition as presenting for diagnosis. To simplify later discussion, the etiological classification of the five hundred cases may be presented in tabular form.

The group classifications are intended only for convenience and are in some measure arbitrary. Other groupings would be equally open to criticism and would fail to embody the features upon which emphasis is to be placed. The figures presented have but minor statistical value as indicating relative incidence. The group of ear cases, for example, constitute a portion of a study on otosclerosis which has been reported in part elsewhere (3). Other individual conditions present beginnings of studies which are now under way, as the Parkinsonians, the primary anaemias, and the leukaemias. Where selection has thus been exercised the number of cases recorded is of no significance. All of them, however, fall in one of the several categories outlined above.

Following the practice of the earlier papers in this series, a few of the physical measurements and significant statistics are collated in tabular form. To conserve space, the weight, chest

TABLE II

PHYSICAL MEASUREMENTS AND "VITAL CAPACITY" COMPARISONS

No.	Sex		Obs.	Age	Height	Sitting Height	Chest	Weight	Lung Volume
	M.	F.							
500	37%	63%	High	78	193	100.5	125	145.0	5600
			Low	4	113	60	53.5	19.2	300
			Average	**36** yrs.	**164** cm.	**87** cm.	**79** cm.	**60.2** cm.	**2950** cc.
Sitting Height Index 0.530		"Vital Capacity"		High (%)			+56	+109	+23
				Low (%)			—23	—40	—89
				+Average (%)			**+9**	**+18**	**+5**
				%			52	44	15
Area 1.66 sq. m.				—Average (%)			**—7**	**—12**	**—24**
				%			48	56	85
				Net Average			**+2**	**+1**	**—20**

and lung volume comparisons, using Dreyer's and West's standards under limitations already described, are also included.

The female dominance in the sex proportion has already been commented on in the earlier papers where, in the endocrine conditions discussed, it is even more striking. That individual conditions fail to show this disparity (Syphilis: males, 28; females, 29) is lost in the method of presentation. Diseases of the female pelvis obviously play no part in our figures (see Table I). We are inclined to the belief that a more frequent resort to medical aid on the part of the female is a definite although unevaluable factor.

The ages show a wide range, although in fairness it must be said that young children play but a small part in the series. This is determined in no small measure by the inability of the young to give that measure of co-operation which is essential for the performance of the tests. Further, the standards for childhood lack the clarity of outline determined for the adolescent and the adult. We have experienced the greatest difficulty in obtaining opportunity to study healthy children in order that such criteria might be established. For this reason we have been obliged, with much regret, to limit our studies, in largest measure, to those groups in which normal performance and the deviations induced by disease have both been defined by actual test and observation.

Extrapolation is always hazardous and peculiarly so when one must bridge so active a period of physiological readjustment as the early years of puberty. In the present series, only eleven children are less than eleven years of age, and of these but two are less than eight. These were two boys, respectively four and six, but both presenting unusual mental maturity coupled with an even more unusual capacity for obedience. In both cases the tests were entirely successful. The popular encouragement to self-expression in early childhood has deprived us vociferously of a number of potential studies.

The several physical measurements show an equally wide range. The maximum weight record of 145 kgm. was that of a so-called normal giant, a man of huge frame and complete normality of physical function. The averages throughout are definitely normal when due allowance is made for the relative sex influence in determining certain ratios. For example, the chest measurement predicted from the sitting height would be 82.8 cm. for the male and 75.5 cm. for the female (Dreyer). Weighting for relative sex influence, the predicted value becomes 78.2 cm., while the observed rounded average is 79 cm. This serves to illustrate both the absorption of large individual variations in any average computation and equally, the significance attaching to the variations (when presented by a single group), even though they be of small magnitude. This latter point has been stressed in the earlier endocrine papers. In them also has been emphasized the greater significance of relative values when comparisons are with standards making allowance for certain of the fixed variables. The so-called ''Vital Capacity'' comparisons embody this principle and the data gather an added import. The cases in the series show a rough equality in over- and under-weight. The former is the smaller group but is free from the natural limitation implicit in those below prediction; as a result, it balances in amount what is lacking in number and the net average deviates but 1 per cent away from prediction. The chest measurements, as is to be expected, parallel those for weight. With the lung volume, however, there is a sharp and significant departure from the normal. Only 15 per cent exceed prediction and then only to an inconsiderable amount. The net average shows a drop of 20 per cent from predicted to observed values. As has been previously stated, we have found Dreyer's male ''A'' and female ''B'' standards most nearly to conform to normal American relationships. In a recent monograph Myers (4) has presented a most valuable summary of the influence of cardiac and pulmonary disease on this quantity. He concludes that lung volumes falling 15 per cent or more below the predicted level require careful examination. In addition to a variety of significant pathological states influencing lung volume unfavorably, he records others, chiefly residua, which are devoid of clinical import. Malingering and lack of co-operation are cited as factors to be reckoned with.

In our own experience the second of these assumes a very marked significance and one of us has emphasized its influence as clearly indicated where a long series of observations are made on the same patient (5). The asthenia of severe illness, irrespective of character, is a powerfully inhibiting influence (eight cases of primary anaemia averaged —41 per cent, and six of leukaemia —38 per cent), and low values are to be interpreted as due in part to weakness. In the present compilation, the importance resides in the low average produced by such a variety of conditions of which cardiac and respiratory conditions are only a small part.

As the cases of this group were studied primarily for their simulation of endocrine conditions or the possible presence of an endocrine element in the etiology, a brief comparison may be made with the results of the several endocrine series.

TABLE II-a

"VITAL CAPACITY" COMPARISONS

	Gland				
	Function	Pituitary	Thyroid	Ovary	Adrenals
Weight	—	+22	+10	+ 5	—11
	±	+12	+ 6	—	—
	+	+ 7	— 3	—	—
	Weighted Average	+14	+ 7	+ 5	—11
Lung Volume	—	—19	—22	—19	—18
	±	—19	—22		
	+	—16	—39		
	Weighted Average	—18	—24	—19	—18

The obesity of the pituitary and the emaciation of the adrenal cases show marked divergence from the non-endocrine average. The tendency of the hypofunctional endocrine states (exclusive of the adrenal) is here evidenced.

With the lung volume measurements, on the other hand, only the thyroid exceeds the loss shown by the non-endocrine group. It is striking that the subjects of adrenal deficiency in whom asthenia is a uniform and highly significant observation, show slightly smaller loss than does the group under discussion. The lack of representative character determined by the meager number of adrenal cases may conceivably be balanced against the appreciable number of approximately normal individuals which tend to raise the average in the non-endocrine group.

The results of analyses and tests using the urine as the medium of response, are collected in Table III.

TABLE III

URINE MEASUREMENTS

Urine Analysis		Phenol Sulphone Phthalein		Nitrogen Partition	
Observation	Amount	Observation	Amount	Observation	Amount
Volume ... High (cc.)	4600	1st Hour ... Average (%)	35	Total N_2 ... Average (gms.)	**9.00**
Low (cc.)	300	2nd Hour ... Average (%)	20	Urea N_2 ... Average (%)	**81.1**
Average (cc.)	**1210**	Total ... Average (%)	**55**	Uric Acid ... Average (%)	**2.3**
		High	90	Ammonia ... Average (%)	**3.8**
		Low	8	Creatinin ... Average (%)	**4.5**
Spec. Grav ... High	1.037			Residual ... Average (%)	**8.3**
Low	1.005			% = or >9% ... (%)	48
Average	**1.018**				
		Urea Curve			
Albumin (%)	26	Normal (%)	**54**	Miscellaneous Tests	
Casts (%)	19	Delayed (%)	**11**		
Sugar (%)	9	Progressive (%)	**9**	Amylase Index, Average	14
"Urobilinogen" (No.)	4(1)	Low (%)	**26**	Salol, Average (min.)	71

While certain of the cases showed a marked polyuria, the average elimination conforms to normal figures, as does that for the specific gravity. The appreciable percentage of cases showing albuminuria and casts includes not only the established kidney cases but numerous others in which nutritive disturbances, faulty posture, and similar factors are operative. The cases exhibiting glycosuria are interesting and significant. It is understood, of course, that no cases of pancreatic diabetes are included. They were excluded from the endocrine studies for reasons that have already been discussed and naturally may form no part of a group of non-endocrine diseases. The allocation of the glycosurias to the major etiological headings is informative.

TABLE III-a

Condition	No. of Cases
Lesions Central Nervous System	13
Psychoses	4
Syphilis	8
Gall Bladder Disease	4
Normal Pregnancy	1*
Asthma (Adrenalin)	1
Primary Anaemia	2
Leukaemia	2
Malignant Neoplasm	2
Total	37

The remaining eight cases were scattering and no direct cause of the glycosuria was ascertained. Malnutrition was not impossibly the cause in the majority of them. Alcoholism may have been a factor in two cases. While certain of these conditions are generally recognized as causative of low-grade glycosuria (lesions of the brain, gall bladder, pregnancy, etc.), comment may be permitted on certain others. In our experience, a slight glycosuria is the frequent accompaniment of syphilitic infection even when no evidence can be obtained of active involvement of the nervous system. It is also noteworthy that one-third of the leukaemic cases, one-fourth of the primary anaemias, and one-third of the cancer cases presented the same condition.†

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*Glucose and not Lactose.

†Since the subject is shortly to be considered elsewhere, no further discussion is necessary at this time.

As the endocrine cases (exclusive of the thyroid) show an incidence of nearly 25 per cent, the significance of the present observation is patent.

Reverting to Table III, another interesting observation lies in the occurrence of a positive ''urobilinogen'' test in four cases of primary anaemia. This test was first offered as an indication of liver disease but was shown by us to occur frequently in pituitary disorders. That positive response is not conditioned solely by the presence of urobilinogen in the urine, is highly probable. Like many color tests, the reaction is probably not specific.

The Phthalein test offers nothing distinctive, the low normal value agreeing with the findings in the endocrine series. The provocative urea curves equate well with the urine findings, one-fourth of them showing poor elimination. Low values do not always imply a lessened kidney permeability, as a number of cases of partial protein inanition exhibit the same phenomenon. Whether an analogy to the condition postulated in Folin's theory (6) of tissue absorption of ingested carbohydrate is operative here, remains to be determined. The relatively normal salol value is a modest bit of evidence for relative kidney integrity as it measures this function primarily, the indication of the level of gastric motility depending on normal elimination.

The Nitrogen Partition and its implications have been discussed in detail in the earlier papers. In brief, a residual nitrogen fraction in excess of 9 per cent is to be regarded as an evidence of disturbed metabolism. While high values are found in all endocrine conditions and their incidence is frequent,† we regard the phenomenon as an indication of the influence of ductless glands on general metabolism rather than a pathognomic sign of endocrine malfunction. The data given above offer strong supporting evidence for this contention. While the average level is below the limit set for normality, in practically half of the cases it has been exceeded. The allocation of these cases to the several etiological groups is interesting.

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†The endocrine relationships are as follows:

TABLE III-b

Gland	*Pituitary*	*Thyroid*	*Ovary*	*Adrenal*
Residual N_2, Av.	9.4%	10.3%	9.1%	9.3%
%=or > 9%	51	61	48	56

Only in subjects of thyroid and adrenal involvement does the incidence exceed significantly that of the non-endocrine subjects, although all of the glands exhibit averages above the normal limit.

TABLE III-c

Etiology of Non-Endocrine Cases Exhibiting High Urinary Residual Nitrogen.

Etiological Group	Total Cases	No. with High N_2	Per Cent
Primary Infections	53	27	51
(a) Secondary to other disease		9	
Psycho-Neurotic States	60	36	60
Lesions of Cent. Nerv. System	44	26	59
Epilepsy	9	7	78
Park. Syn. and Paral. Agit.	10	4	40
Syphilis	42	24	57
Diseases of Kidney	50	29	58
(a) Secondary to other disease		24	
Anaemia (prim. and sec.)	10	7	70
Leukaemia (myel. and lym.)	6	6	100
Tumors (mal. and benign)	12	8	67
Goiter, non-toxic[1]	8	4	50
Normal	18	0	0
		211[2]	

NOTE—Total of 235 cases in 489 recorded.

[1] Concerning the propriety of the inclusion of this group, see text.

[2] The remaining 24 cases were too widely scattered to possess any etiological significance.

The high incidence in epilepsy, leukaemia and the tumor group is striking though it exceeds, in degree only, several of the other groups which show a frequency of over one in every two cases. As an evidence of metabolic disturbance we feel the case established; as a differential diagnostic point it is wholly non-specific. Undoubtedly had this investigation extended to other morbid states, additional conditions would be included. It is perhaps important that the so-called diseases of metabolism

TABLE IV

BLOOD CHEMISTRY (AND SEROLOGY)

	High	Low	Average	Deviation	Per Cent
Non-Protein Nitrogen. (mgm.)	128	11	**32**	> 35 mgm.	20
Urea Nitrogen (mgm.)	75	6	**15**	> 17 mgm.	20
Uric Acid (mgm.)	7.1	1.7	**3.5**	Net(1) =or > 4 mgm.	10
Creatinin (mgm.)	5.0	1.0	**1.5**	—	—
Residual Nitrogen (mgm.)	>50	< 5	**15.2**	—	—
Sugar (mgm.)	133	68	**97**	>120 mgm. < 80 mgm.	4 3
+Wassermann %			**6**		
+Kahn (presump.) number			**10**		
+Spinal Fluid number			**8**		
+Schwartz-McNeil number			**1**		

(1) All cases demonstrating Nephritis and Gout have been deleted.

are not represented in the group. The term "metabolism" is a comprehensive one and includes a myriad of interrelationships. A possible dominance of the nervous system might be deduced from these figures but the seeming relationship may be only an arithmetical artefact. Many thousands of diverse observations would be necessary to resolve the question with any measure of certainty.

As the precursor of the urine, the blood in its chemical aspects may next be considered.

Since renal disease plays a not inconspicuous part in this series, it is to be expected that high values will appear in the individual observations. Inspection of the superior limits shows values compatible with severe but not terminal nephritis. Twenty per cent show values for non-protein and urea nitrogen in excess of the conventional normal.

Significant from the differential standpoint is the relatively low incidence of high uric acid values. A high blood uric acid with relatively normal non-protein nitrogen has been observed in pituitary malfunctions, and in the proven absence of nephritis and gout may possess definite diagnostic value. The relative infrequency in the non-endocrine group enforces the observation.

Another significant feature is the small percentage of blood sugars falling outside the conventional normal limits. Further, the maximum individual deviations observed are of the order of ±10 to 15 per cent, and those were recorded in single cases only. If the average values be taken for the several quantities, the entire picture is one of the most rigorous normality. Six per cent of the cases showed positive Wassermanns, confirmed in the ten most recent cases by a similar response to the Kahn presumptive test. Incidentally, the correlations in the series are complete.

In addition, eight other cases gave positive results, indicating neurosyphilis, in the examination of the spinal fluids. For obvious reasons, lumbar punctures were not a part of the invariable routine, but were performed wherever history, physical examination, or laboratory picture gave evidence of a possible specific condition. A few Schwartz-McNeil tests were made, giving a positive response in only one case. Of the forty-two cases in which syphilis was the primary condition, thirty-eight were confirmed by the positive serological findings, while in the remaining four the diagnosis was equally certain although treatment had obliterated the serum response.

The character and amounts of the several form elements of the blood is always important, and in not a few conditions determine the final diagnosis. Our own observations are assembled in Table V.

TABLE V

BLOOD MORPHOLOGY

General Examination		Amount	Differential Count(1)		Per Cent
Haemoglobin	High (%)	>100	P. M. N. Neutrophiles	Average	**61**
	Low (%)	15	% >75%		6
	Average (%)	87			
Erythrocytes	Average (10^6)	4.85	Lymphocytes	Average	**31**
			% >33%		43
Color Index		0.90	Eosinophiles	Average	**2**
Leucocytes	Average(1) (10^3)	8.1	Net(2) % =or >3%		15
			Endothelials	Average	**6**

(1) Omitting data of 6 cases of Leukaemia.

(2) Cases in which a non-endocrine cause of eosinophilia was demonstrated, have been deleted.

In compiling these averages, the few cases of primary anaemia have been included but, as is stated in the footnote, the cases of leukaemia were deleted from the leucocyte average. Typical observations in this group were 92,300 and 82,900 in two representative cases. The inclusion of these would change the average by nearly 10 per cent and render it by so much the less representative of the entire group. Taking the picture presented by the average values, the general impression is one of normality. The haemoglobin value is somewhat low, but the cases composing the group included many in which slight secondary anaemia is a common feature. This is also reflected in the red count.

The differential count, from its relative character, is perhaps somewhat more significant. The lymphocyte average is normal in contradistinction to that in the endocrine cases as shown in Table V-a.

TABLE V-a

Lymphocyte Count Averages.

Gland	Pituitary	Thyroid	Ovary	Adrenal
Lymphocyte %	36	37	35	37
%=or > 33%	59	60	56	50

While these values exceed those of the non-endocrine group, the differences are not great. Further, while the latter series averages less than the arbitrary "normal," nearly half of the cases in the group exceed this limit. An allocation of these cases to the several general diagnostic groups is presented in Table V-b.

TABLE V-b

Etiology of Non-Endocrine Cases with Lymphocytosis.

Etiological Group	Total Cases	Cases with Lymphocyt.	Per Cent
Primary Infections	53	26	49
(a) Infection (secondary)	..	10	..
Psychoneurotic States	60	36	60
Lesions of Cent. Nerv. System	44	19	43
(a) same, secondary	..	1	..
Epilepsy	9	2	22
Park. Syn. and Paral. Agit.	10	9	90
Syphilis	42	19	45
Diseases of Kidney	50	24	48
(a) same, secondary	..	26	..
Anaemia (primary)	8	5	63
(secondary)	2	0	0
Leukaemia (myel. and lymph.)	6	3	50
Tumors (mal. and benign)	12	3	25
Goiter (non-toxic)	8	3	38
Normal	18	0	0
		186	

NOTE—Total of 215 cases in 489 recorded. The remaining 29 cases were widely scattered.

The same general diagnostic groups are the representatives in this compilation as in that dealing with the high residual nitrogen. Further, in certain members the correlations are definite, as in the groups of infections, the mental and nervous disease group, and less strikingly in the syphilitic, cardio-renal groups, and those cases with lesions of the central nervous system. Equally, if not more significant are the divergences from parity. For example, the epileptic group shows a lymphocytosis far less frequently than a high residual nitrogen (78 per cent against 22 per cent), while the Parkinsonians (with Paralysis Agitans) exhibit more than double the incidence. Five in eight of the primary and neither of the two established secondary anaemia cases show it. There is a markedly lower occurrence of a lymphocytosis in the tumor group.

Whatever the exciting cause, it is obvious that two widely different mechanisms must be involved in the production of the two phenomena. As the matter contains certain possibilities, a still more detailed analysis may be permitted. Certain diagnostic groups have been shown to exhibit a practically equal incidence of the two aberrations, while in others there is a well defined diffrenece. The relative frequency in which both are shown by the same individual has been determined.

TABLE V-c

Correlation of (a) High Residual Nitrogen
with
(b) Lymphocytosis in Non-Endocrine Group.[1]

Etiological Group	1 Total Cases	2 With a, b or Both	3 With a+b	4 Per Cent +Cases	5 Per Cent All Cases
Infections	89	58	14	24	16
Psycho-Neurotic States	84	53	19	36	23
Lesions of Cent. Nerv. System	47	35	11	31	23
Epilepsy	10	7	2	29	20
Park. Syn. and Paral. Agit.	10	10	3	30	30
Syphilis	56	31	12	39	21
Diseases of Kidney	90	82	21	27	23
Anaemia	12	8	3	38	25
Leukaemia	6	6	3	50	50
Tumors	12	8	3	38	25
Goiter, non-toxic	8	6	1	17	13
Miscellaneous	..	..	10	..	..
			102		

[1] Both Primary and Secondary conditions are included.

In the various correlations, leukaemia leads easily, which is probably attributable to the fact that all cases show a high residual nitrogen. Obviously the correlation depends also on the proportion of the lymphatic type. Comparing frequency with incidence of one or the other condition (column 2 with 4), syphilis with low and anaemia and tumors with moderate frequency show a high correlation. On the other hand, the Parkinsonian (and Paralysis Agitans), kidney and goiter cases, show high incidence and moderate or low correlation. Lesions of the central nervous system show a moderate frequency and a like correlation. The nervous and mental diseases with low, and epilepsy with moderate frequency show respectively moderate and low correlation. The infection group is consistently low throughout.

The authors offer no theory to explain these phenomena at this time but confine themselves to presenting the facts. One more comparison is suggestive, namely, the relative incidence in the several endocrine groups in comparison with the present diverse assembly.

Gland	N_2 Increased Lymph, Normal	N_2 Normal Lymph, Increase	Both Increased
Pituitary	19%	27%	33%
Thyroid	23%	22%	39%
Ovary	21%	28%	28%
Adrenal	31%	25%	25%
Total Endocrine[1]	20%	27%	33%
Non-Endocrine	27%	23%	21%

[1] Weighted for relative representation.

The greater measure of correlation in the endocrine group is apparent.

Reverting for a moment to Table V, it will be seen that not only is the average eosinophile value a normal one, but the percentage exhibiting eosinophilia is much less than with the endocrine group, particularly in the adrenal and pituitary cases.

A very definite influence on the respiratory metabolism is exercised by the members of the endocrine group. While the striking changes produced by aberrant thyroid function has tended to minimize the attention devoted to the other members of the concert, they all participate and determine certain highly characteristic deviations from the predicted normal. Improvement in accuracy and simplicity of determination of the magnitude has extended the study into numerous other fields, and it is recognized today that a variety of non-endocrine causes may produce deviations in the basal rate which equate in magnitude with those of endocrine origin. In any method of differential diagnosis employing basal metabolism tests, the non-endocrine become equally important with the endocrine cases and must be reckoned with primarily in any interpretation of data. Many of the early data relative to the basal rate in disease derives from duBois and his associates (7) at the Russell Sage Institute of Pathology, although Magnus Levy (8), beginning in 1894, established trends of deviation in a large number of disease conditions. Later workers have added much, and there is today a steadily growing and extensive literature which has been well reviewed in several recent monographs.*

The influences that have been observed can best be discussed after consideration of our own data. Because they are pertinent to the basal rate determinations, certain concomitant observations are likewise recorded.

The observed rates vary from +49 per cent, which would equate with a moderate hyperthyroid condition, to —25 per cent, a level which might be associated with failure of any of the four principal endocrine glands (pituitary, thyroid, ovary, adrenal).†

On the other hand, the average of nearly half of the cases showing rate above prediction is only +7 per cent, while the somewhat larger group falling below the base line gives the same minus average. The net average deviates but 1 per cent from prediction. Further, 80 per cent of the cases fall within the conventional normal zone. With the exception of a few conditions which have been previously demonstrated to influence respiratory metabolism, the great majority of the cases fail to produce deviations which could confuse an endocrine diagnosis.

To specify the disturbing influences and indicate their extent, an analysis of our own data may be made and discussed

TABLE VI

RESPIRATORY METABOLISM

Observation	Amount	Observation	Amount
Basal Metabolism		Blood Pressure	
Deviation........High (%)......	+49(1)	Systolic.........Average (mm.).	**124**
Low (%)......	—25	% =or >150 mm...............	11
+Average (%).................	+ **7**	% =or <110 mm...............	24
%..............................	44	Diastolic........Average (mm.).	**73**
—Average (%).................	— **7**	% =or >100 mm...............	6
%..............................	56	% =or < 65 mm...............	27
Net Average..................	— **1**		
% above +10%................	6	Pulse Rate........Av. (per min.)..	**77**
% between +10% and —9%....	80	% =or >80.....................	38
% =or below —10%...........	14	% =or <70.....................	30
Alveolar CO_2.......Average (mm.).	**39**	Respiration Rate..Av. (per min.)..	**15**
% >35 mm.....................	45	% =or >20.....................	13
% =or <30 mm.................	7	% =or <10.....................	9
		Temperature......(deg. F.).......	**98.2**

(1) Lymphatic Leukaemia.

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*See among others Graefe (9), Boothby and Sandiford (10), McCann (11) and Selected Chapters in "Endocrinology and Metabolism" (12). See also the numerous publications of W. O. Atwater, F. G. Benedict, and their associates for many fundamental studies.

†For reasons earlier discussed, the pancreas has played no part in this study.

TABLE VI-a

ETIOLOGICAL ALLOCATION OF BASAL RATES

Pathological Condition		High	Low	Basal Rates		Total	Group Average
Group	Detail			+	—		
Infections	Tuberculosis(1)	+12	—19	6 = + 5	11 = — 9	17 = — 4	— 3
	Atrophic Rhinitis	+11	— 3	3 = + 9	1 = — 3	4 = + 6	
	Arthritis	+ 8	— 8	6 = + 3	12 = — 5	18 = — 2	
	Gall Bladder Inf.	+ 6	—12	2 = + 4	6 = — 8	8 = — 5	
	Focal Infection	+ 6	—12	3 = + 2	2 = — 9	5 = — 2	
Psycho-Neurotic States	Neuroses	+12	— 8	10 = + 7	11 = — 5	21 = + 1	— 1
	Psycho-Neuroses(2)	+10	—10	11 = + 5	12 = — 5	23 = — 1	
	Psychoses	+17	—21(3)	7 = + 8	8 = — 8	15 = — 1	
Central Nervous System	Lesions of Central Nervous System	+19	—20(4)	19 = + 9	25 = — 7	44 = ± 0	± 0
	Epilepsy	+14	— 9	4 = + 8	5 = — 5	9 = + 1	
	Parkinsonian Syndrome and Paralysis Agitans	+105(5)	— 3	8 = +30(5)	2 = — 3	—	
Kidneys	Diseases of Kidneys	+15	—17	13 = + 7	9 = — 7	22 = + 1	± 0
	Cardio-Renal Disease	+20	—20	14 = + 7	14 = — 8	28 = — 1	
	Syphilis	+17	—23	20 = + 6	22 = —11	42 = — 3	— 3
Blood	Anaemia (primary)	+ 7	—25	5 = + 4	3 = —14	8 = — 3	—
	Leukaemia	+49	— 4(6)	5 = +31	1 = — 4	6 = +25	—
	Tumors	+14	—15	6 = + 7	5 = — 8	11 = ± 0(7)	— 1
	Non-Toxic Goiter	+10	—11	3 = + 4	5 = — 6	8 = — 2	
	Obesity	+ 8	—11	6 = + 3	6 = — 4	12 = — 1	— 1
	Asthma	+ 9	—10	3 = + 4	8 = — 6	11 = — 3	— 3

(1) Afebrile. Average Temperature =98.4.
(2) One case omitted (+29) where patient restless and value obviously too high.
(3) Marked malnutrition Next low case —9.
(4) Brain Tumor.
(5) See text (6 cases = +11).
(6) During remission period. High rates observed later.
(7) Basal Rate not obtainable in one case.

with running comment on previously recorded observations. It should perhaps be emphasized that the component cases of the groups here presented have been demonstrated to be free from endocrine complication. Where such exists, the case has been listed under the endocrine focus participating. To illustrate, a certain small percentage of arthritic cases have well established thyroid failure and improve on thyroid medication. Similarly, we have demonstrated that gall bladder (and liver) disease may accompany thyroid failure and seemingly be closely associated with it in a causal or resultant relationship. The coincidence of the two conditions has been remarked by others. The simultaneous presence of an endocrine malfunction, coincidently with a well-defined non-endocrine disease, may well account for some of the contradictory observations recorded in the literature.

Tuberculosis in its early stages at least and without a marked febrile condition, seemingly tends toward a normal or slightly depressed basal rate. This is in accord with the earlier reports. The high rates are usually but the expression of the influence of fever, as duBois has so clearly shown. Graefe's few severe cases would seem to offer an unexplained exception.

Uncomplicated arthritis apparently arising from infective processes is rigidly normal in this series. The low values which are occasionally recorded are possibly due to an endocrine element. The same is true for cholecystitis, although malnutrition may operate in this condition to lower the basal rate. The group which we have conventionally designated as ''Infections'' shows no evidence of significant departure from prediction.

In the next group of nervous and mental states two complications may arise. First, some cases presenting one or another of these conditions may have a definite endocrine complication which seemingly is causal (see paper on Thyroid in this series, l.c.). That the speculative practice of ascribing all mental disease to endocrine aberration is unwarranted, the cases listed above will prove. Again at the risk of over emphasis it may be said that the final diagnosis rests on a very complete clinical and laboratory study in which each observation is interpreted in the light of numerous others. The endocrine complicity is neither included nor excluded on the basis of a single test, and certainly not on that of a single opinion. If this current study of approximately two thousand cases (supported by nearly two thousand more since this compilation was begun) can be taken as warranting a tentative opinion, the percentage of psychotic cases which can be proven to derive from endocrine malfunction is not large. Equally, however, a definite number do demonstrate an endocrine etiology and this factor must be considered. The second complication is implicit in the nature of the case. Slight movement will exercise a wholly detrimental effect on the accuracy of the test, and nervous instability may determine muscular efforts too slight to produce gross movement but ample to vitiate the measurement. We have deleted two of our cases for this reason, and regard many of the retained values as probably somewhat above the truth. Due attention to this disturbing element and the education of the patient by repeated tests as a means of correcting it, will give fairly representative values. We feel, in the cases reported, that gross error has been eliminated.

So comprehensive a term as ''lesions of the central nervous system'' naturally embraces a wide variety of conditions. In some of the brain tumor cases the lowered rates were possibly attributable to pressure influencing the pituitary unfavorably. In one case which we were privileged to study and which gave all of the typical evidences of pituitary disease, autopsy demonstrated that the neoplasm localized outside of the gland but had produced a sufficient intracranial pressure seemingly to determine a typical pituitary dysfunction. The cases here listed gave no evidence of pituitary participation other than the possible influence on the basal rate. The group of epileptics is also normal, although in several cases degenerative changes had resulted from a long standing condition.

The group of Parkinsonians (including a few cases of paralysis agitans) are extremely interesting. Very high values were obtained in a few cases but we were fortunate enough to secure several in which the syndrome was in its incipiency.* These cases showed values which were normal or, at the worst, but slightly above the normal level. This seems to confirm the opinion of Magnus Levy (13), although by no means controverting the later opinion of Graefe (14). In this connection, a case of paralysis agitans, observed in the course of another study, offers information of value. The patient, a man in the late fifties and with a very pronounced tremor, was studied at two-week intervals for a considerable period. His prevailing rate lay with surprising uniformity between +60 per cent and +70 per cent. At the time of one test in the middle of the series, it was noted that his tremor was perceptibly less, and on this day the rate dropped to +24 per cent. When next seen the tremor had resumed its wonted course and the rate was +64 per cent. A single observation of this character is interesting even though it cannot be regarded as decisive.

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*The authors wish to express their thanks to Dr. N. H. Garrick for his interest and courtesy in securing these cases for us.

Our renal cases show the general normality that has been recorded by others. Edema was not a complication in this group. The cardio-renal group practically repeats the kidney observations, although the extreme limits are slightly wider. Individual cases, however, may well have some slight superimposed effect (low protein diet, for example, in a considerable number of these cases) which will in summation exceed the normal limits. We feel that this explains our own cases showing a hypofunctional level. The actual numerical values of the low readings are more significant than the high, for reasons that have already been discussed.

The syphilitic cases show a definite downward tendency. Twenty-two cases average —11 per cent, and in this group are several with rates of about —20 per cent. When taken in conjunction with the influence on carbohydrate metabolism frequently exercised by this disease, it is evident that syphilis may simulate endocrine disease in some measure. While the serological tests should preclude frequent grave error, the necessity for their performance is patent.

Primary anaemia has severally been recorded as ranging from about —20 per cent to +30 per cent, both extremes suggesting a possible endocrine involvement. In our own very small group but one case falls outside relative normality, and as this is to be discussed later, comment may be postponed.

The tumors, both malignant and benign, fall reasonably within the normal zone. Boothby and Sandiford report one case of Hodgkin's disease with a rate above +20 per cent. Our two cases gave readings of, respectively, +3 and — 15 per cent.

The basal rates of the non-toxic goiter cases offer one definite warrant for their inclusion in the non-endocrine group.

Physiological obesity, as was earlier shown by Means (15) exercises no detectable influence on the basal rate.† The asthma cases are recorded as the condition is, from time to time, referred to an endocrine origin. The present group gives no evidence of any hormonic influence.

Reverting to Table VI, it will be noted that while the averages for the Blood Pressure are entirely normal, an appreciable percentage (about one-fourth) show hypotensive levels which might suggest endocrine disease. The Pulse Rates show nearly 70 per cent outside of the range of from 70 to 80. The other findings are essentially normal.

Alveolar carbon dioxide exhibits a normal average, nearly half the cases above the conventional lower limit of normality and but 7 per cent showing a tension suggestive of acidosis. With the number of kidney cases in which a retention acidosis is possible, the value observed is reasonable. While the general picture is a normal one, enough has been shown to indicate that individual cases may far exceed normal limits, and by a fortuitous combination suggest an endocrine malfunction, the nonexistence of which can be demonstrated only by a comprehensive study.

The sugar (galactose) tolerance is the sole remaining laboratory test permitting presentation in tabular form.

TABLE VII

Galactose Tolerance

Observation	Unit	Male	Female	
Tolerance Dose.........High....	gms.	40	40	
Low.....	gms.	5	5	Summary
% above Normal.............	%	3	0	
Average Deviation............	%	**+33**	—	% > Normal......... **1** % = Normal......... **41**
% equal Normal..............	%	37	43	% < Normal......... **58**
% below Normal.............	%	60	57	Av. Deviation(1) >N... **+33**
Average Deviation............	%	**—47**	**—43**	Av. Deviation(1) <N...**—45**

(1) Not weighted for numbers.

The test is one of great differential significance, as there is not only an intrinsic sex difference, but each of the important endocrine glands exercises a definite and charactertistic influence on the amount of the sugar capable of utilization. In the table given above, slightly less than 40 per cent of the cases are considered. The data here reported are derived from the routine work of a consulting diagnostic service. The sugar test, which requires two or three days for performance, is performed only when its indications are essential for the establishment of a diagnosis.

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†The cases here listed averaged 101.2 kgm. and 59 per cent above predicted weight.

Of the cases examined, less than half showed a normal tolerance.* Only two cases showed a tolerance above normal, and those were both advanced cases of chronic interstitial nephritis. Lessened permeability of the kidney rather than heightened carbohydrate tolerance is patently the cause of this observation.

The allocation of the remaining one hundred and twelve cases showing a lowered tolerance bears directly on the thesis.

Of parallel observations but a few need be mentioned. Bauer (16) first suggested the use of galactose as the basis of a tolerance test, applying it to liver conditions. His primary contribution was followed by numerous studies, which have been summarized by Wörner (17). Later studies have supplemented and confirmed the earlier opinions. Offenbacher (18) has demonstrated that galactose and levulose are both influenced by liver integrity, while glucose, on the other hand, seemingly is not. Bauer, in a later paper (19), records observations in cases of syphilis and of malignant neoplasm, using a uniform test meal of 40 grams. As an elimination of less than 3 grams was regarded by him as a negative response, his conclusion of normality in these conditions is erroneous. The writer's own observations show that a significant percentage of syphilitics show a definitely lowered tolerance, and similar findings in malignant neoplasms are confirmed, among others, by Friedenwald and Gross (20) and Langston (21). The observations of Lorenz (22) would seem to indicate a lowered tolerance in certain psychotic states, although Barrett and Serre (23), in dementia praecox, were unable to demonstrate any consistent abnormality in sugar

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*As has been stated in the previous papers, the male tolerance is unvarying and at 30 grams. The female, on the other hand, is normal with 20 grams in the prepubertal period, passes during puberty by degrees to 40, the normal adult level, and at the menopause may maintain the adult 40 or more usually, or recede to 30 grams. Pregnancy lowers the tolerance first to 30 and later to 20 with restoration to the normal adult level with the resumption of sexual rest. For this reason, tolerances are expressed in percentage deviation from the individual norm.

TABLE VIII

Etiological Allocation of Cases with Abnormal Tolerance
112 Cases with Lowered Tolerance

Group	
Central Nervous System[1]	43[2]
Psycho-Neurotic States[1]	15
Syphilis	15
Primary Anaemia	7
Leukaemia	4
Tumors (malignant)	3
Asthma (Adrenalin med.)	2
Gall Bladder (Liver)	7
Hypertension	4
Total	100

NOTE—Of the 12 remaining cases, all show a depression of only 10 grams.

Two cases with increased Tolerance (males at 40) had advanced Chronic Interstitial Nephritis.

[1] See Table I for composing members.

[2] Percentages are not given as all of the cases in a group did not receive the sugar test.

tolerance. Hirose (24), Strauss (25), Wagner (26), and others, have noted depressed tolerance for galactose in the neuroses. O'Hare (27) found abnormal tolerance in one-half of a series of hypertensive cases. Davidson and Allen (28) have shown a lowered tolerance in head injuries, and Kasanin and Garfield (29) observed decreased tolerance, associated with encephalitis, in adults, although the opposite obtained with children.* Richard Bauer (30), using 40 grams of galactose as a test meal and regarding an elimination of less than 2 grams as negative, could find no influence on the tolerance in primary anaemia. With the wide range of conditions listed in which a lowered tolerance is a possible or even a probable observation, it is obvious that the test, while of great differential value, requires a variety of supplementary tests for its proper interpretation.

It will be remembered from Table III, that 9 per cent (45 cases) showed glycosuria. While the metabolism of glucose and of galactose, in some measure at least, bespeak different mechanisms, the lowered tolerance for galactose offers a possible explanation of the glycosurias observed. The whole question of non-diabetic glycosuria* is implied in the observations of this and the several endocrine series. Seemingly many agencies operate to lessen the power of the body to utilize carbohydrate. While pancreatic diabetes is the prototype, there are many other conditions producing the same end result but engendered by wholly different causes and operating under wholly different laws. The end result of glucose in the urine is the only point they have in common.

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*In many of the papers cited above, tolerance was determined by the shape of the sugar curve. Comment has already been made upon the lack of quantitative significance of the single sugar curve. It may be regarded, however, as offering some qualitative evidence of the relationship of the exciting dose to the individual tolerance.

PART II

CLINICAL SECTION

Introduction. Although the differential diagnosis of endocrine and non-endocrine conditions usually depends upon laboratory findings for its confirmation, the attempt of the clinician should always be toward simplification, since in many instances there is neither time, money, nor facilities for an elaborate study of the patient presenting an obscure disease picture. It is under such conditions that so much "experimental" endocrine therapy is employed, to the detriment of that branch of medicine and often to the patient. Therefore the present analysis was undertaken to determine what symptoms and signs are significant in separating endocrine from non-endocrine conditions, and to what extent that differentiation may be made without the aid of laboratory examinations.

It is well perhaps to state at the outset that so far as differential diagnosis is concerned, the non-endocrine conditions which have come to us for metabolism studies may be separated into two groups: namely, those in which the history and a careful physical examination disclose a typical picture, and those in which the history does not indite one organ or system and the physical examination is significant, largely because it affords only "negative" or non-specific evidence. In the former group, laboratory examinations may furnish corroborative evidence in regard to diagnosis, and valuable aid in treatment, but they are not essential for the identification of the disease present; while in the latter group, laboratory tests must be relied upon, in the present state of our knowledge, to disclose the facts by means of which the diagnosis is reached. For example, disease of the heart, or circulatory system, can almost always be satisfactorily diagnosed by means of the patient's story and the clinician's examination, and while electrocardiograms, blood pressure measurements and radiograms of the heart may furnish comforting assurance that the diagnosis is correct, they seldom modify it or the treatment essentially. In contrast, in primary anaemia, diabetes, asthma, syphilis often, and disorders of metabolism practically always, the laboratory evidence is necessary if the diagnosis is to be certain and treatment effective.

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*A paper is shortly to appear treating this matter in detail.

In this section, therefore, emphasis is placed on diseases of the latter group, since they are the ones most often confounded with one another. It is not often, in our experience, that infectious endocarditis and thyrotoxicosis are confused; the difficulty, as judged by the character of the patients referred to us, lies in separating neuroses of neurogenic origin from those secondary to metabolic disturbances, or in recognizing tertiary syphilis, early lesions of the central nervous system, anaemias and leukaemias as the cause of the patient's condition. The diseases which are most frequently confused with endocrine disorders may be found in table (I) (v. s.) which comprises a diagnostic grouping of the patients examined by us who showed no convincing evidence of endocrine disorder but in whom evidence of other functional disturbance or organic disease was found.

The table shows that the principal non-endocrine conditions encountered were, in their order of incidence, lesions of the central nervous system, cardiovascular diseases, psychoneuroses, deafness, chronic infections, and syphilis. The high incidence of vascular disease and deafness in this group is artificial, due to factors already pointed out.

A more exhaustive analysis of the diagnostic groups remaining serves to show why they are frequently mistaken for endocrine disturbances. Thus, of the central nervous system lesions, the greatest number were post-meningitic or post-encephalitic arrests of development, with a lesser number of epileptics and patients with the Parkinsonian syndrome. The differentiation between post-meningitic or post-encephalitic arrests of development and those due to mild thyroid failure, is from clinical evidence alone, often impossible, and since the former conditions are almost irremediable and the latter responds dramatically to treatment, it is only proper to give the patient the benefit of any existing doubt, and to determine, by means of such laboratory investigations as are necessary which condition really exists. So far as epilepsy and paralysis agitans are concerned, their frequent occurrence in our series is due not to mistaken initial diagnoses but to a commendable effort to detect, if possible, a curable cause for the symptom complex presented. In epilepsy, our studies have occasionally brought to light some associated disturbance of metabolism, the correction of which has resulted in an arrest of the convulsions, while in the case of Parkinson's syndrome they have served to disprove the theory that the condition is in some way due to ''hypoparathyroidism.''

Under the heading ''psychoneuroses'' are included neuroses and psychoses as well as true psychoneuroses. Whether or not the patients were correctly allocated to their proper sub-group, it is a significant fact that the symptoms were no more varied or severe in these ''non-endocrine'' patients than in those showing incontrovertible evidence of associated endocrine disturbance (1, 2). We have been forced to conclude that every patient exhibiting symtoms of neurosis, psychosis or psychoneurosis deserves a careful medical endocrine study before the condition is ascribed to ''neurogenic'' or psychogenic causes. We do not wish to be understood as ascribing every neurosis or psychosis to disturbed endocrine function: but we do wish to emphasize the point that only by careful metabolic studies can such a condition, either associated or causal, be eliminated in case of any given patient.

In the group of the chronic infections, tuberculosis heads the list. Little comment is needed on this point. The difficulty of differentiating incipient phythisis from thyrotoxicosis has been pointed out by many writers, but it needs repetition in these days of diagnosis by means of a single basal metabolic rate to the exclusion of repeated physical examinations. It is perhaps significant that focal infections, not associated with disturbed metabolism, are so rare in our series. Attention has already been called in our papers on thyroid ovarian and pituitary disturbances, to the high incidence of focal infections in association with those conditions: the material presented here tends to support by its negative character our suggestion that focal infection certainly, at times, produces its deleterious effects via the endocrine system.

The presence of a large percentage of syphilitics in a series of patients suspected of endocrine malfunction is to be expected, and serves to illustrate the protean character of lues. It serves also to make clear the necessity for serological tests on all patients sufferings from obscure conditions.

One other group of patients deserves comment here, that labeled in the table ''disorders of metabolism.'' Though less important, numerically, it comprises two conditions often wrongly charged against faulty endocrine function, ''malnutrition'' meaning underweight, and obesity. Our studies of these patients confirm the opinion of other writers that in by no means all obese patients can a metabolic disturbance be demonstrated and to a certain extent controverts the theory frequently encountered that a pluriglandular preparation is a good ''tonic'' for any individual who is underweight.

To summarize briefly the conclusions to be drawn from Table I, it may be said that, in considering the possibility of disturbed endocrine function in any patient, tuberculosis, syphilis, sequellae of meningeal infections, and ''idiopathic'' malnutrition and obesity must be ruled out by adequate objective evidence, while the possibility of disturbed endocrine function as a contributing or causal factor exists in any case of epilepsy, neurosis or psychosis, a possibility demanding adequate objective evidence for its proper evaluation.

An analysis of the histories and physical examinations of patients in the non-endocrine group justifies our emphasis upon the importance of the clinical examination of the patient, since it reveals certain facts which are of considerable help in separating, at least tentatively, the ''endocrine'' from the ''non-endocrine'' individual. This, although we believe that in the majority of instances the clinical evidence must be substantiated by correlated laboratory tests before the examiner can properly treat the patient with an endocrine preparation. It must be recognized that many individuals can be spared the expense and bother of metabolism studies if the examiner gives sufficient time and thought to the results of his personal examination. A brief discussion of the most important clinical findings in this series is therefore necessary.

TABLE IX

Family History

Malignant Neoplasm	19.6%
Diabetes	7.0%
Thyroid Disease	3.0%
Tuberculosis	18.0%
Mental Disease	8.0%
Epilepsy	0.6%
Venereal Disease	1.0%
Blood Diseases	1.8%
Cardio-Vascular Diseases	13.8%
Diseases similar to that of Patient	19.2%

Inheritance. The importance of inheritance in determining a patient's tendency toward certain diseases is still a matter of argument. With the growth of laboratory methods of diagnosis the "family history" was at one time almost disregarded, but more recent opinion seems likely to give it a place of considerable importance as an aid to diagnosis. Familial tendency to endocrine disorders is generally recognized, and our own studies (g. v.) furnish evidence in support of this idea. They also indicate that this familial tendency is more marked in endocrine than in non-endocrine diseases, since in the former there is a "positive" family history in approximately 40 per cent of the cases, while in only 19 per cent of the latter group was there a history of a near relative who suffered from the same disease as did the patient. These figures are not quite comparable since the term "endocrine disorders" embraces a large number of clinical conditions, but the preponderance indicates that careful inquiry into the patient's family history is likely to furnish evidence valuable enough to justify the effort involved. It should be pointed out, however, that the inheritance is not always specific. The fact that a parent or sibling has thyroid disease is no evidence that the patient's symptoms are due to abnormal function of that gland, but does furnish strong presumptive evidence that they may be associated with some endocrine disorder, if no organic pathology is found to explain them.

Sex. As regards this factor, our figures do not support the thesis that the female sex is peculiarly liable to endocrine diseases. Practically all of the gonad subjects (95 per cent), 73 per cent of our patients with thyroid disease and 60 per cent of those with pituitary disorders were females, but the possible significance of these figures is nullified by the fact that 63 per cent of our patients with non-endocrine disorders were also females. The only conclusion justified by these findings is that, for reasons not pertinent to this study, women predominate in hospital clinics, and that in our material, the percentage of males with endocrinopathies was not significantly smaller than that with non-endocrine disease. We believe that endocrine disturbances are more frequently encountered in men than is generally supposed.

TABLE X

AGE

Diagnostic			Years					
Group	1-10	11-20	21-30	31-40	41-50	51-60	Over 60	Aver.
Infections	0	6	10	14	15	11	0	38
Psycho-Neuroses	1	3	22	14	11	6	3	36
Lesions of Central Nervous System	8	18	26	12	11	4	3	29
Metabolism	1	6	9	8	5	1	5	36
Cardio-Vascular	1	6	9	11	11	8	15	44
Blood	0	2	2	2	2	6	3	46
Tumors	1	0	8	2	5	1	3	37
Syphilis	2	9	6	11	7	4	4	35
Eye	0	0	1	0	1	1	2	50
Ear	1	8	22	12	10	3	1	33
Skin	1	3	7	2	0	4	0	31
Gastro-Intestinal	0	1	3	1	5	0	0	34
Pelvic	0	0	2	3	0	1	0	34
Asthma	0	2	0	1	4	2	2	44
Miscellaneous	0	0	0	0	1	1	0	49
Normal	2	2	5	4	3	1	1	30
Total	18	66	132	97	91	54	42	36
Per Cent	3.6	13.6	26.4	19.4	18.2	10.8	8.4	

Age. On the basis of division by decades, there is no significant difference in the age incidence of endocrine disturbances and those non-endocrine conditions which are most frequently confused with them. All are characteristically diseases of adolescence and early adult life, though no age period is free from them. A few of the non-endocrine groups such as that of cardiovascular disease show some deviation but are not those in which confusion is most likely to occur.

Fertility. A study of sterility in "endocrine" and "non-endocrine" patients brings to light some interesting facts. Of our "non-endocrine" patients 26 per cent of the matings were

TABLE XI

MARITAL HISTORY AND FECUNDITY

Diagnostic Group	Married No.	Married %	Dur. Av.	Conceptions	Children	Miscarriages	Abortions	Infertile No.	Infertile %
Infections	32	57	16	74	63	11	0	5	16
Psycho-Neuroses	31	52	13	60	44	11	5	9	29
Cent. Nerv. System	30	37	14	60	47	12	1	12	40
Metabolism	17	49	19	48	28	19	1	5	29
Cardio-Vascular	39	64	22	125	99	15	11	5	13
Blood	12	71	25	31	24	7	0	3	25
Tumors	10	50	12	12	10	2	0	4	40
Syphilis	21	49	17	68	52*	15	1	9	43
Eye	4	80	31	15	14	1	0	0	0
Ear	18	32	13	30	27	3	0	5	28
Skin	3	18	17	9	8	1	0	0	0
Gastro-Intestinal	5	50	9	10	8	1	1	1	20
Pelvic	5	83	12	11	9	2	0	2	40
Asthma	6	55	23	14	10	4	0	2	33
Intoxications	2	100	23	8	4	1	3	0	0
Normal	7	39	12	18†	9†	5	1	2	29

*One with 15 and one with 10; remaining 19 had only 27 children.
†Three pregnant.

infertile, as compared with 39 per cent in the thyroid, 36 per cent in the pituitary and 41 per cent in the ovarian group, evidence that a history of sterility is an important suggestion of endocrine disturbance. Further analysis of the non-endocrine group shows that the conditions most frequently associated with sterility include two which are difficult to differentiate from endocrine disorder, syphilis with 43 per cent and lesions of the central nervous system, with 40 per cent infertile. The only other conditions showing the same incidence of putative sterility are pelvic disease (40 per cent), tumors, benign and malignant (40 per cent) and asthma (33 per cent). The coincidence of pelvic disease and syphilis with sterility is well known and easily understood; that of asthma, tumors and central nervous disease we believe has not been previously recognized, and we have no explanation to offer for our findings. From the point of view of internist, obstetrician and gynecologist, however, it is important to realize that in searching for the cause of a sterile mating, a possible endocrine factor must be considered as important as any other single cause.

Catamenia. Seventy per cent of our female patients in the non-endocrine group began to menstruate between their twelfth and fourteenth years, as compared with 45 per cent of the "thyroid group" and 65 per cent of the "pituitary group." In other words, non-endocrine diseases do not, in the majority of girls, cause significant delay of the menarche; but do cause such

TABLE XII

CATAMENIA

A. Onset	Before 12	12-14	After 14	Total
	22	212	65	299

B. Period	Diminished	Flow Normal	Increased	Total
Irregular 85				
Diminished	7	16	11	34
Both	2	4	3	9
Increased	15	17	10	42
Total	24	37	24	85
Regular 214	41	138	35	214
Grand Total	65	175	59	...

delay in over half of those with thyroid failure and in approximately one-third of those with disturbed pituitary function. These figures naturally derive from groups composed, in significant measure of women whose endocrinopathy was present during the years of maturation. In certain much larger series compiled by one of us (A. W. R.) the differences are less striking, but in each of these were a large number of women whose history and physical evidences indicate an inception of the endocrine condition, years after the transition to maturity had taken place. In these larger groups, the ovarian cases show by far the largest proportion of women maturing within conventional normal limits, a possible indirect evidence either of the lesser part played by the gonad before maturity or equally to be interpreted as a lessened incidence of lowered glandular activity in the prepubertal years. Though the absolute figures differ, practically the same ratios hold for physical development in general, as indicated by abnormal weight and height, while the incidence of delayed mental development was practically the same in endocrine and non-endocrine conditions. As far as our evidence goes, arrested or delayed mental development is as often due to meningeal infections or birth trauma as to disturbed function of the glands of internal secretion. Over 70 per cent of the non-endocrine group show regularity of the menses, while the endocrine groups show a definitely lower incidence. The pituitary and ovarian cases show a tendency toward a lengthened interval while the thyroid group contains from four to five times as many women with complete irregularity as do any of the others.

The normal amount of the flow is somewhat elastic in its definition. Making due allowance for this fact, however, we find that while all of the groups show 50 per cent or more falling inside conventional limits, the division of the remainder between flow that is "scanty" and that which is "profuse" approximates a parity in every instance.

TABLE XIII

AGE OF ONSET OF CHIEF COMPLAINT

Period	Incidence			
	Non-Endocrine	Pituitary	Thyroid	Gonad
0-10	14%	2%	2%	9%
11-20	24%	30%	19%	32%
21-30	20%	22%	20%	31%
31-40	18%	17%	17%	16%
41-50	13%	20%	17%	7%
51-60	7%	8%	18%	3%
Over 60	4%	1%	7%	2%

DURATION, NON-ENDOCRINE

Less than 1 year	12.8%
From 1 to 5 years	43.4%
From 6 to 10 years	20.8%
Over 10 years	23.0%

Age of Onset and Duration of Chief Complaint. The statements from which the above data derive are a somewhat uncertain quantity in which a subjective element is or may be dominant. For example, the high degree of incidence shown in the first three decades in the ovarian cases may be a real datum or no more than an expression of the egocentricity of the sufferers from this particular disorder. Barring the relatively high value for the incidence during the first decade in the patients forming the non-endocrine group, the major sections show a definite degree of correlation with those of the pituitary series. The gonad cases concentrate in the first three decades, while those patients presenting thyroid disease show a substantially constant recognition with low incidence only in the first and last stadia. In the light of the subjective element, it is hard to say how meaningful these figures may be. With the large percentage of normal catamenial histories in the ovarian group, the fact that two-fifths of them date their chief complaint from the first two decades, engenders a certain scepticism. The 14 per cent in the first decade of the non-endocrine cases undoubtedly arises in the large number of young patients with disorders

TABLE XIV

PAST HISTORY

Measles	83.8%
Mumps	48.2%
Chicken Pox	47.4%
Whooping Cough	59.4%
Scarlet Fever	26.2%
Diphtheria	16.6%
Typhoid	9.0%
Malaria	3.4%
Pneumonia	13.6%
Influenza	29.8%
Rheumatic Fever	3.2%
Arthritis	5.4%
Tonsil or Sinus, Infections	9.8%
Venereal Infections	7.8%
Nervous Diseases	3.0%
Encephalitis	3.4%
Renal Disease (acute)	1.2%

OPERATIONS

Tonsils and Adenoids		35.4%
Sinuses		3.0%
Infected Glands		4.6%
Eyes		3.6%
Nose		10.0%
Hernia		2.0%
Appendix		20.4%
Gastro-Intestinal		8.4%
Ulcers, etc.	2.2	
Gall Bladder	3.0	
Haemorrhoids	3.2	
Tumors		3.8%
Pelvic		28.8%
Dilatation and Curettage	12.3	
Repair and Suspension	5.4	
Ovariectomy (one)	6.0	
Hysterectomy	3.8	
Caesarian Section	1.3	
Joint and Spine		5.4%

affecting the nervous system who were referred for the possible existence of a causal endocrine factor. This magnitude compared with the proportion of children in the pituitary and thyroid groups may offer a first rough approximation of the relative causation of physical or mental retardations.

The period of duration in the non-endocrine group does not differ substantially from our records in the endocrinopathies. This factor, like the age of onset, is influenced unduly by non-controllable influences. We offer them as the opinions which they are, not as facts.

TABLE XV

COMPLAINTS

	Chief (as given by patient)	Combined Primary and Secondary
Headache	10.2%	57.6%
Vertigo	4.2%	30.0%
Fatigue	24.0%	36.8%
Faintness	3.4%	10.6%
Convulsions	4.2%	5.6%
Nervousness	9.6%	27.4%
Pain	16.0%	30.8%
Paralyses	3.6%	
Tremors	2.2%	
Mental Disturbances	5.0%	
Underweight	2.0%	
Overweight	5.8%	
Disturbances of the		
Eye	4.4%	
Glasses		55.4%
Pain		8.4%
Poor vision		16.2%
Visual aberrations		13.6%
Ear	14.0%	
Ache		11.4%
Deafness		28.6%
Tinnitus		17.6%
Nose	1.0%	
Colds (frequent)		22.2%
Catarrh (chronic)		7.0%
Epistaxis		7.0%
Discharge		5.4%
Obstruction		9.0%
Mouth (canker)		4.0%
Teeth		
Poor		18.2%
All extracted		10.4%
Throat		
Sore (frequent)		30.0%
Cardio-Respiratory System	5.6%	
Dyspnoea		35.2%
Palpitation		28.0%
Pain		17.4%
Cough		19.8%
Cardio-Vascular System	11.8%	
Gastro-Intestinal System	11.6%	
Nausea		21.4%
Vomiting		18.2%
Pain		15.8%
Jaundice		6.6%
Constipation		41.2%
Diarrhoea		4.0%
Poor Appetite		31.4%
Genito-Urinary System	2.8%	
Frequency		15.2%
Nocturia		19.8%
Urgency		5.2%
Dysuria		7.8%

TABLE XV—Continued

COMPLAINT

	Chief (as given by patient)	Combined Primary and Secondary
Menstrual Function	6.0%	
Delayed Onset		21.7%
Irregularity		28.3%
Dysmenorrhoea		24.7%
Skin	4.6%	
Arthritis	6.4%	
Paraesthesias		17.6%
Ataxia		3.8%

Previous Illnesses. The one outstanding feature in this table is the significantly greater incidence of tonsillar infection in the endocrine than in the non-endocrine group. Judged by the same standards, the former showed about 75 per cent with convincing evidence of present or past tonsillar infection, the latter, 45 per cent. We have called attention to the possible relation of chronic tonsillar infection to endocrine disease in previous papers (2) but the findings become doubly significant in the light of our present records. It is probably also significant that while the number of tonsillectomies previously performed was not significantly different in the two main groups, the incidence of unrecognized tonsillar infection was much greater in those with endocrine disturbance than in that with non-endocrine disease. At first thought these findings may seem paradoxical, but we believe that the explanation is that constant absorption from the unrecognized chronic tonsillar infection may be a potent cause of deranged endocrine function in any individual with an inherited predisposition of those organs. As a corollary, we believe that failure of the patient's general condition to improve following removal of definitely infected tonsils in every instance should raise the suspicion of a residual endocrine disturbance.

No other diseases in the patients' past histories show any particularly significant variation in incidence in the various groups studied; in fact, the percentage of occurrence of illness other than focal infection is almost identical for endocrine and non-endocrine groups.

Present Illness. Exhaustion. As has been pointed out in a previous paper, the characteristic symptom of thyroid dis-that nervous instability, so characteristic of lowered ovarian function, as possibly evidenced during the menopause and, in a different manner, in thyroid disorders, is conspicuous by its absence in the patients with pituitary disturbance. No explanation of the fact is at present available, and the presence or absence of ''nervousness'' is hardly a dependable differential symptom. It may be stated, however, that its presence as a definite symptom should logically raise the question of an underlying metabolic error as its cause.

Vertigo was not a frequent chief complaint in our ''non-endocrine'' patients, but demands discussion because of its serious import when it is an outstanding symptom. Drury's recent paper (33) discusses it in detail but it needs to be emphasized that from the internist's point of view, vertigo demands a careful search for organic disease of the central nervous system as the first step in the diagnosis. To this end, ability to use the ophthalmoscope and a reasonable experience in interpreting its findings, is essential to every internist and general practitioner.

As compared with our endocrine patients, the incidence of vertigo as a presenting symptom is greater in the pituitary group and not significantly different in any of the others. As a definite but secondary symptom it is surprisingly frequent in thyroid disturbances, and in them, was occasionally so severe as to simulate closely an intracranial tumor. In the ovarian group, its incidence was trivial. Neither the character nor severity of a vertigo, therefore, is sufficient to define its cause in all cases, and the possibility of an endocrine etiology must always be kept in mind while examining a patient with that complaint. Such a possibility should not, however, be entertained until lesions of the central nervous system have been rigorously ruled out.

Menstrual Disturbances were not frequent among our ''non-endocrine'' patients, occurring in only 6 per cent of this series, although from 25 to 30 per cent reported dysmenorrhoea and irregularity. These figures are in striking contrast to those for the thyroid and pituitary groups, in which the incidence was 59 and 54 per cent, respectively, while the ovarian cases head the list with 14 per cent presenting this condition as a chief complaint and show, in addition, 42 per cent with irregularity and 68 per cent with dysmenorrhoea. Excepting demonstrable pelvic disease, the only non-endocrine diseases frequently associated with disturbed menstruation are tuberculosis, the anaemias and leukaemias, conditions which, as we have already pointed out, often closely simulate endocrine disorders. If these conditions be certainly eliminated, a study of endocrine function is indicated in any patient with disturbed menstruation, a fact emphasized by Graves (34) and others. In the absence of definite pelvic disease, surgical treatment for menstrual disorder is justified only when a possible endocrine disturbance has been eliminated—not by one "basal" metabolism test, but by a careful survey of general and special metabolism, a fact not yet sufficiently appreciated by the medical profession as a whole.

TABLE XVI

Physical Examination

Development		
Good	70.4%	
Fair	21.4%	
Poor	8.2%	
Nutrition		
Good (normal)	35.8%	
Overweight	23.6%	
Underweight	40.6%	
Skull Abnormalities		9.0%
Hair		
Scant on Vertex	12.6%	
Excess on Body	12.8%	
Abnormal Pubic Distribution	4.8%	
Eyes		
Pupillary Abnormality	7.2%	
Abnormal Reflexes	9.6%	
Strabismus	4.0%	
Nystagmus	1.6%	
Exophthalmos	1.2%	
Deafness*		20.2%
Nose		
Septum Deviation	13.8%	
Discharge	4.2%	
Tender over Sinuses	2.0%	
Teeth		
Poor condition	38.2%	
All extracted	14.2%	52.4%
Doubtful Tonsils*		16.4%
Enlargement of Thyroid		10.2%
Chest		
Asymmetry	6.2%	
Earlier Rickets	2.0%	
Lungs		
Dullness	8.4%	
Abnormal Sounds	16.6%	
Râles	12.2%	

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*See report on special examination.

TABLE XVI—Cont.

Heart		
Enlarged	5.8%	
Murmurs	15.6%	
Abnormal Rate	9.6%	
Abdomen		
Mass	1.8%	
Tenderness	15.6%	
Hernia	4.8%	
Fluid	0.8%	
Enlarged Liver		2.6%
Palpable Kidney		1.8%
Enlarged Spleen		1.2%
Genital Abnormalities		2.4%
Adenopathy		
Cervical	18.4%	
Axillary	2.2%	
Inguinal	6.4%	
Skin Eruptions		27.8%
Varicosities		8.6%
Spine		
Scoliosis	10.2%	
Lordosis	6.0%	
Kyphosis	3.0%	
Tenderness	5.0%	
Abnormalities of Extremities		25.4%
Neuro-Muscular		
Knee Jerks increased	11.4%	
Knee Jerks diminished	13.8%	25.2%
Other abnormal Reflexes	6.6%	
Romberg positive	4.2%	
Clonus positive	2.2%	
Misc. tests positive	2.4%	
Loss of sound conduction	1.6%	
Mental Abnormalities		16.0%

There is an unfortunate tendency to belittle the physical examination in these days of instruments of precision and laboratory diagnosis. Nowhere is this tendency more prevalent or fraught with greater danager than in the realm of endocrine disease. It is perfectly true that the physical findings alone seldom furnish evidence adequate for the identification of disturbed endocrine function but it is equally certain that omission of a most careful and complete physical examination has led, and will always lead, to disastrous mistakes in the interpretation of laboratory findings. Reference to the case protocols appended to this monograph will show that non-endocrine disease may simulate an endocrine disturbance in every detail but one, and that one will be found frequently in the physical examination. This is especially true as regards diseases of the nervous system, the anaemias, tuberculosis and syphilis.

In these conditions, careful observation should elicit evidence at least strongly suggestive of organic disease, and such suggestions of endocrine disorder as are encountered should be disregarded until the examination is complete. The presence of thyroid enlargement, for example, is no indication of disturbed thyroid function, and if such significance be attributed to it, the examiner may easily overlook incipient tuberculosis, adenopathy suggestive of syphilis or leukaemia or may interpret parasthesias as suggestive of thyroid disturbance when they are in fact the early signs of a pernicious anaemia.

Even those findings which are ordinarily regarded as significant of endocrine disturbance must be regarded with caution, since all of them may be encountered in patients in whom, at the time of examination at least, no evidence of disturbed metabolism can be found. The fact that they may well be residua of previous endocrine disorder does not justify their acceptance as criteria of the present metabolic level.

An example of the danger of interpreting physical findings as diagnostic of present endocrine disturbance is afforded by obesity. Because many patients with thyroid or pituitary hypofunction are obese, there is a tendency to reason (?) that all obese patients are suffering from thyroid or pituitary failure, and to dose them accordingly, often with disastrous results. That such a deduction is entirely fallacious is proven by the fact that practically a fourth of our "non-endocrine" patients were significantly overweight and that a considerable number of them had at one time or another been given thyroid, or other endocrine substance as a part of their reduction treatment. While obesity, especially if it be distributed asymmetrically, may raise the question of endocrine disturbance, it certainly cannot be accorded any weightier significance.

Similarly, abnormal height can be suggestive only, and even thyroid enlargement and exophthalmos were found in patients in this series, the former in 10.2 per cent, the latter in 1.2 per cent. The incidence of tonsillar infection was significantly less in our "non-endocrine" than in our endocrine group, occurring in only 16.4 per cent of the former. Focal infection, therefore, occurring in patients complaining of symptoms suggestive of disturbed metabolism, on the basis of probability is suggestive of the presence of an associated endocrine disturbance, rather than an argument against it.

Disease in the heart and lungs was far more frequently encountered in our ''non-endocrine'' than in our endocrine patients. In the former, evidence of pulmonary abnormality was present in 37.2 per cent of patients, while it was conspicuous by its absence in those showing significant metabolic disturbances. Cardiac disease was encountered in 31 per cent of our non-endocrine patients. The possibility of mild cardiac insufficiency as a cause for fatigability, vertigo, cold hands and feet, indeed for all the symptoms so commonly encountered in an ''endocrine'' history, must be constantly borne in mind.

Abdominal involvement would hardly seem to simulate endocrine disorders, yet 23 per cent of the patients in the series under consideration referred to as probably suffering from endocrine disturbance, showed evidence of definite intra-abdominal disorders, possibly overlooked and certainly discounted through over-enthusiastic attention to certain endocrine ''stigmata.''

It would also seem that evidences of disease of the central nervous system often fail to receive the consideration due them, as 25.2 per cent of our ''non-endocrine'' patients had abnormal knee jerks, 17 per cent showed other abnormal reflexes, and 22.4 per cent, irregular pupils, disturbed pupillary reflexes, nystagmus or strabismus. Once more it seems necessary to emphasize the point that the presence of any of these findings demands the abandonment of interest in endocrine function until proper examination has disclosed or eliminated disease of the central nervous system.

Apparently those conditions, especially in their early stages, are frequently confused with ''functional disorders'' since of the patients in this series submitted to complete neurological examination 61 per cent showed definite neurological conditions, and lumbar puncture gave ''positive'' results in 44 per cent of the patients upon whom it was performed.

The entire list of special examinations found necessary in the study of these ''non-endocrine'' patients are enumerated above, and it is only possible to emphasize here those which we have found most often necessary. These comprise complete neurological examination, examination of the upper respiratory passages and appendages, the many forms of radiologic study,

TABLE XVII

SPECIAL EXAMINATIONS

Observation	No.	No. +	% +
Audiogram	159	145	91
Bacteriological	40	8	20
Barany	84	18	21
Biopsy	5	5	100
Cardiac	125	41	33
Cardiogram (Electro)	46	26	57
Dental	16	15	94
Endermal	28	15	54
Genito-Urinary	24	16	67
Laryngological	93	39	42
Liver Function	14	9	64
Lumbar Puncture	23	10	44
Lungs	36	15	42
Neurological	182	111	61
Orthopaedic	51	44	86
Otological	43	26	60
Pelvic	95	28	29
Psychiatric	46	43	93
Rhinological	93	35	38
Skin	25	23	92
Surgical	23	13	56

SPECIAL EXAMINATIONS (EYE)—323 EXAMINATIONS

Abnormal	
Discs	43.7%
Fundi	8.7%
Pupils	10.2%
Fields	43.0%
Blind Spots	54.2%

ROENTGENOGRAMS

Part	No.	No. +	%
Skull	247	55	22
Sinuses	59	37	63
Teeth	57	39	68
Heart	181	39	20
Lungs	207	79	38
G. I. Tract	37	22	59
Gall Bladder	6	6	100
Graham	9	6	67
Kidneys	10	6	60
Joints	53	34	64
Spine	44	15	34

and ophthmological examinations, the latter affording perhaps more valuable aid than any other single examination in the diagnosis of the more obscure conditions encountered in this series.

In conclusion, it seems worth while briefly to restate what we have learned from the study of our "non-endocrine" patients.

First. We believe that endocrine and non-endocrine conditions often simulate each other so exactly that only by correlating complete clinical and laboratory study is differentiation possible.

Second. When clinical examination discloses evidence of organic disease, it must take precedence over any evidences of metabolic disturbance in determining the diagnosis.

Third. While the history and physical examination are essential to the differentiation of non-endocrine and endocrine conditions, clinical examination is often insufficient for the establishment of a correct diagnosis, and must be supplemented by such laboratory studies as may be necessary to reveal the status of metabolic efficiency.

In a succeeding paper will be published a series of protocols of non-endocrine cases simulating endocrinopathies.

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Reprinted from ENDOCRINOLOGY, The Bulletin of the Association for the Study of Internal Secretions, 1214 Wilshire Medical Bldg., Los Angeles, California, Vol. 13, No. 2, March-April, 1929, Pages 109 to 143.

STUDIES OF THE ENDOCRINE GLANDS. VII (b)

Protocols of Non-Endocrine Cases Simulating Endocrinopathies

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In a preceding paper* of the series of which this communication forms a part, the importance of differentiating true endocrinopathies from other cases simulating them was discussed. Herewith are presented a number of case protocols in illustration of some of the interesting categories that have come to our attention.

GROUP I. CASES SIMULATING SOME TYPE OF THYROID DISEASE

CASE B-329.—PARALYSIS AGITANS SIMULATING HYPERTHYROIDISM. The patient was a man 57 years of age, emaciated, presenting as his chief complaint a coarse tremor of the extremities, difficulty in speech, and pain in the muscles of the legs and shoulders. Eight years previously he had remarked a slight hesitancy in raising his right hand, coupled with a pain in the right shoulder. During the following year he developed extreme fatigability, and one year after the onset of the condition he noted an intention tremor of the hand, which progressed unfavorably during the next two years. He then noticed a slight dragging in the right foot and was told that he had an abscess on the brain. His reaction to this news was a complete nervous breakdown during which all of his symptoms were exaggerated. Still another year later he developed pain in the chest, burning sensations in the right leg and right side of back. A winter in California produced a larger measure of comfort, but no real improvement in the symptoms. A few months before we saw him the left side became involved, pain and lameness increased and speech defects appeared. He had lost 15 pounds in the past eighteen months, but there had been an earlier loss in the preceding years of the condition. The face had become masklike, the eyes noticeably staring and the tremor extensive and coarse in both arms and legs.

Family History: The patient's father died of cancer; the remaining history was negative.

Past History: The patient reported the usual children's diseases and an attack of typhoid three years before the onset of his illness. He had been married for 17 years; his wife had borne one child without miscarriage. He complained of some vertigo. The hearing was impaired on the right side and there was a right-sided partial nasal obstruction. He experienced tinnitus, some dyspnoea during the past year and had been constipated for a long time. Some urinary frequency and urgency, marked fatigability as already noted, and occasional cramps.

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*Lawrence, C. H. and A. W. Rowe: This Journal, 13: 109. 1929.

Physical Examination: The patient was a tall, emaciated individual 57 years of age, with a mask-like expression and a marked tremor of all of the extremities. The right pupil was slightly larger than the left, there was a slight divergent strabismus and lateral nystagmus, a minor cervical adenopathy, slight increase in the breath sounds at the right apex, and sluggish knee jerks. A state of tonus in the extremities, and an inability to spread the fingers of the right hand were also noted.

TABLE XVIII

Simulation of Thyroid Disease

1. Paralysis agitans simulating Hyperthyroidism.
2. Myelogenous Leukaemia simulating Hyperthyroidism.
3. Primary Anaemia simulating Hypothyroidism.
4. Lesion of central nervous system simulating Hypothyroidism.
5. Pulmonary Tuberculosis and Epilepsy simulating Hypothyroidism.
6. Pulmonary Tuberculosis referred for Hyperthyroidism.

	1	2	3	4	5	6
Case Number	B-329	B-481	B-552	B-809	B-883	S-1057
Sex	M	F	F	M	M	M
Age (yrs.)	57	50	47	57	13	29
Height (cm.)	176	155	165	182.5	156.5	176.0
Weight (kgm.)	53.4	31.4	43.6	69.8	44.0	53.7
Weight Deviation (%)	—24	—38	—28	—12	—14	—26
Lung Volume Deviation (%)	—43	—33	—32	—13	— 5	—11
Basal Rate Deviation (%)	+105	+49	—25	—15	—20	+ 7
Blood Pressure (mm.)	136/62	112/56	145/72	110/65	102/54	110/58
Pulse Rate (per min.)	72	100	68	56	78	72
Temperature (deg.)	96.8	98.0	99.0	98.0	99.0	98.0
Alveolar CO$_2$ (mm.)	43	41	41	42	44	38
Urine Volume (cc.)	620	510	690	1480	730	2430
Spec. Grav.	1.021	1.028	1.012	1.015	1.010	1.014
Albumin	+	+	0	+	+	0
Casts	0	0	+	+	0	0
Sugar	0	0	0	0	0	0
"Urobilinogen"	0	0	+	0	0	0
Total Nitrogen	6.48	7.91	3.31	10.30	3.32	15.35
Residual Nitrogen (%)	8.3	18.3	13.9	9.4	11.0	7.7
P. S. P. (2 hours) (%)	56	58	..	56	54	63
Galactose Tolerance						
Normal (gm.)	30	30	30	30	30	..
Observed (gm.)	10	10	30	30	30	..
Deviation (%)	—67	—67	± 0	± 0	± 0	..
Blood						
N. P. Nitrogen (mgm.)	33	42	36	33	32	32
Uric Acid (mgm.)	3.3	3.7	7.1	2.9	3.3	3.1
Sugar (mgm.)	109	68	95	89	94	104
Haemoglobin (%)	75	80	30	85	100	85
Erythrocytes (10^6)	5.30	3.70	1.20	4.35	5.41	5.84
Color Index	0.71	1.08	1.25	0.97	0.92	0.73
Leukocytes (10^3)	5.2	82.9	6.7	8.2	9.7	6.8
Neutrophiles (%)	50	5	62	65	46	75
Lymphocytes (%)	44	56	33	23	42	20
Eosinophiles (%)	0	2	0	3	3	1
Endothelials (%)	6	1	2	8	9	4
Misc. (%)	0	*36	3	1	0	0
Wassermann	0	0	0	0	0	0
Spinal Fluid	—	—	—	0	—	—

*Myelocytes.

Laboratory Summary: The patient was 24 per cent below his predicted weight, and there was a marked and significant loss of lung volume. The basal rate was 105 per cent above prediction, systolic blood pressure was normal, but the pulse pressure was large. The pulse rate was normal, body temperature sub-normal. The urine volume was small, elimination poor; albumin present. Protein intake was below a maintenance level. Residual nitrogen showed an upward tendency. The sugar tolerance was much depressed. The blood chemistry was substantially normal. He had somewhat low haemoglobin and a distinct relative lymphocytosis. The blood calcium was definitely depressed; blood coagulation time somewhat retarded. Radiograms of the skull, sella and sinuses were negative. A Barany test was requested, but it was felt unwise to attempt it in view of the patient's physical condition. An audiogram showed a definite loss of hearing in both ears. The eye examination gave sluggish pupillary reactions, yellowish discs, enlarged blind spots, and a slight loss in the form fields. Neurological examination defined the condition as a true paralysis agitans.

Discussion: The whole general picture here contains, superficially at least, many suggestions of a hyperthyroid condition. The patient's loss of weight, tremor and slight but definite exophthalmos, were suggestive. The high basal rate, large pulse pressure, lowered sugar tolerance, definitely lowered lung capacity, were all consistent with a definite degree of thyroid overactivity. His high basal rate derived, of course, from the muscular tremor; the lowered sugar tolerance from a lesion of the central nervous system connected with his disability. A review of his laboratory tests without the clinical picture would inevitably have led to a diagnosis of hyperthyroidism, the only contradictory feature being the normal pulse rate. This case is one in which the laboratory work was of no great significance. The clinical examination determined the diagnosis, and the laboratory work was of value only in its ability to eliminate the presence of some intercurrent condition.

CASE B-481—MYELOGENOUS LEUKAEMIA SIMULATING HYPERTHYROIDISM. The patient was a woman of fifty, referred for study, offering abdominal pain as the chief complaint. This latter had occurred suddenly a week prior to admission and the examination by her physician demonstrated a splenomegaly.

Family History: A prevalence of heart disease in several immediate relatives was the only point worthy of notice.

Past History: The patient reported the usual ailments of childhood, a severe attack of influenza at the time of the epidemic, and pneumonia two years previously. An appendectomy eight years previously had corrected the frequent attacks of nausea and vomiting from which the patient had previously suffered. She had been married for 26 years and had borne one child by operative delivery. There was no history of miscarriages. Following the birth of the child there had been rare but severe attacks of vertigo. Of later years the patient complained of loss of hair. The eyes were said to fatigue easily. There was an earlier history of earache and discharging ears. Recently nasal obstruction had developed, with slight epistaxis on blowing the nose. A number of teeth had been removed. She had had marked dyspnoea for several years; had been extremely fatigable for about the same period and had severe night sweats during the past winter with a gradual loss of weight over a period of four years. She reported some nocturia and had noticed that the urine was very dark during the past year. The onset of catamenia was at 16 and the function was regular and normal up to the birth of her child. Following this there was an occasional period of metrorrhagia, usually with pain. There had been an abrupt menopause at the age of 46. She had suffered from leukorrhea since the establishment of the menses. She was disposed to date all of her difficulties from the birth of her baby 25 years before, and since that time she had had to work hard and had worried over various domestic problems. She acknowledged a degree of emotional instability and complained of formication and occasional tremors of the hands and arms.

Physical Examination: The patient was a frail, poorly developed and undernourished woman of 50; the ear drums were distinctly thickened, but hearing was seemingly unimpaired. There was some crusting in the nares, a number of teeth were missing and the remainder were in poor condition. The tonsils were slightly enlarged. There was a slight increase in tactile fremitus in the region of the left scapula, but the lungs were otherwise normal. The heart was apparently of normal size, the sounds somewhat muffled, no murmurs were remarked; there was a slight sclerosis of the peripheral vessels. The abdomen was slightly distended on the left side, and a large tumor mass, apparently the spleen, was demonstrated. There was also some hepatic enlargement. There were some telangiectases on the extremities. The skin was pallid, and there was a slight yellowish perspiration of unpleasant odor which stained the bed linen. There were superficial lymph nodes, large and hard, all over the body. There was a suggestion of a positive Babinski, bilaterally, the abdominal reflexes were rather less active on the left, the remaining routine neurological observations were normal.

Laboratory Summary: The patient was 38 per cent underweight and showed a significant loss of lung volume. The basal rate was 49 per cent above prediction with rapid pulse, somewhat low systolic blood pressure, and relatively large pulse pressure. The urine was scanty and contained albumin. The residual nitrogen fraction was over 100 per cent above the normal. The sugar tolerance was markedly depressed. The non-protein nitrogen of the blood was above the normal. The blood sugar value as reported was low but this was undoubtedly due to the rapid loss of blood sugar after the removal of the blood, which is characteristic of the leukaemias. The blood morphology gave a characteristic picture of myelogenous leukaemia with 36 per cent myelocytes and a white count of over 80,000.

Ear Examination: No evidence of disease was found beyond the loss of hearing already noted.

Pelvic Examination: The fundus was normal in size, somewhat fixed, and manipulation produced pain. There was laceration of the cervix.

Nose and Throat Examination: The findings were substantially normal.

Neurological Examination: There was no evidence of organic neurological disease. The positive Babinski tests were not confirmed.

Eye Examination: Yellowish discs, enlarged blind spots, and some symmetrical contraction of form and color fields, were noted.

Roentgenogram: The spleen was greatly enlarged.

Discussion: The general laboratory picture here presented, the small urine volume, high residual nitrogen, basal rate well above prediction, rapid pulse, relatively large pulse pressure, increased non-protein and urea nitrogen, normal uric acid, depressed sugar tolerance and significant loss of lung volume definitely suggests a hyperthyroid condition. In this case, of course, the blood picture served as a check on the laboratory findings and prevented an erroneous diagnosis from the laboratory material alone. Naturally the physical examination again prevented error in the classification of the case. With these two exceptions, however, the parallelism between the laboratory observations of the endocrine and non-endocrine conditions is rather striking.

CASE B-552—PRIMARY ANAEMIA SIMULATING HYPOTHYROIDISM. The patient's chief complaint was of increasing fatigability and weakness which had first been remarked a year previously. In the course of a few weeks she developed pain in the legs with numbness and tingling in the extremities. Under medical care there had been temporary improvement, but for several months prior to admission she had been growing progressively weaker and for two months she had been confined to her bed.

Family History: A twin sister had died of primary anaemia. The remaining family history was irrelevant.

Past History: The patient reported the incidence of several of the minor ailments of childhood, scarlet fever and diphtheria during this period, and influenza at the time of the epidemic. Seven years previously she had been curetted for excessive flowing. She complained of a rare headache, some vertigo during the past month, this latter accompanied by photophobia, and some postorbital pain, gave a history of earlier hay fever which had apparently corrected itself spontaneously, and of the earlier removal of several abscessed teeth. During the past month there had been marked dysponoea, and an occasional night sweat. A year previously there had been a rapid loss of weight (18 pounds). She further reported some nocturia, a rare gastric disturbance, occasional constipation, and poor appetite. The catamenia was established at the age of 16, the periods were somewhat irregular with increase in the interspace and an abrupt cessation five years previously at the age of 42, following a three weeks' period of menorrhagia.

Physical Examination: The patient was a fairly well-developed but much under-nourished woman of 47. The lips were pallid and the face had a decided lemon yellow tinge, the tongue was not abnormally smooth and presented a slight tremor on protrusion. There was a loud systolic murmur over the aortic and mitral area, transmitted to the axilla and scapula, as well as a slight diastolic murmur at the apex. A minor cervical adenopathy was remarked. She had a slight kyphosis and lumbar lordosis; coördination was poor in all of the extremities, bone conduction was lost over the tibiae, arms and legs were spastic, knee jerks were increased, certain other reflexes absent, the Babinski was positive, and there was bilateral ankle and patella clonus.

Laboratory Summary: The patient was 28 per cent underweight and substantially below her predicted lung volume. The basal rate was 25 per cent below prediction. The blood pressure showed varying values, that recorded being representative. There was a slightly febrile temperature. The urine volume was scanty; albumin was not observed. Both hyaline and epithelial casts were found in the sediment. The "urobilinogen" test was positive. The sugar tolerance was normal. Non-protein nitrogen was at a slightly high level. The blood uric acid was almost double the normal value. The blood morphology gave a picture characteristic of primary anaemia or one of the simulating conditions. There were two microblasts, thirteen normoblasts, and two megaloblasts, in a count of 200, together with 3 per cent of neutrophilic myelocytes.

Stool Examination: No Bacilli Welchii, no blood, ova or parasites were found.

Cardiogram: The tracings were normal.

Heart Examination: Systolic murmurs were verified and ascribed to the anaemia.

Pelvic Examination: Normal.

Neurological Examination: There was a spastic ataxia syndrome of the lower extremities with Babinski, ankle and patella clonus. Deep sensation was interfered with over the lower extremities, the abdominal reflexes were absent.

Eye Examination: The discs were yellowish in color, the blind spots slightly enlarged.

Discussion: Practically all of the laboratory findings were consistent with hypothyroidism. The low basal rate, naturally, derived from the patient's partial inanition. The urobilinogen, so called, has been observed by us in several cases of primary anaemia and also in those cases of thyroid failure associated with a dysfunctional state of the liver. The somewhat high blood pressure is of the order frequently observed in the late stages of thyroid failure with marked arteriosclerotic changes. The normal sugar tolerance was likewise suggestive, as was the lowered permeability of the kidney indicated in the blood and urine examination. A urea curve gave a much delayed elimination, which again would suggest a thyroid failure. The high blood uric acid was anomalous for the endocrine condition. Of the current laboratory tests the blood morphology was the only one sharply defining in character, and this was supported by the neurological findings. A gastric analysis was not made on this case because of the weakness of the patient and the substantial establishment of the diagnosis by the facts recorded.

CASE B-809—A LESION OF THE CENTRAL NERVOUS SYSTEM SIMULATING THYROID FAILURE. The patient's chief complaint was of persistent headache from which he had suffered since early childhood. At the age of 8 he had an illness which was diagnosed as spinal meningitis in which severe headache was one of the presenting symptoms. This latter persisted after his recovery from the illness. During his earlier life it was occipital and basal in type; of later years it became more frontal. Constipation produced exacerbation, while correction of visual difficulties had been without influence. Some years previous to admission he had been told that there was a deficiency in the blood supply to the optic nerve. A few weeks before this consultation there had been an interval of several weeks during which he had experienced slight vertigo, uncertainty while walking, poor balance, and some slight speech difficulty.

Family History: There were several cases of cancer, probable pulmonary tuberculosis in a sister, and some cardiac disease. One sister also suffered from severe headache which was, however, apparently unassociated with the eyes.

Past History: Beyond the condition noted above, he reported the usual minor ailments of childhood. At the age of 27 he had what was apparently an attack of appendicitis, followed by intervals of pain in the right lower quadrant and a tendency to constipation. Twenty years later the appendix was removed and at this time there was a lysis of adhesions which were quite extensive. Following this operation he had a three-day period of respite from headache which was entirely unique since the onset of the current complaint. At the age of 37 he developed pulmonary tuberculosis, which was pronounced arrested after six years' stay in Colorado. The patient had been married many years; his wife had borne four children with two miscarriages. Other facts in the history are a record of a slight trauma to the head in childhood, a moderate photophobia, frequent nosebleeds in childhood, and an infection of the right antrum, removal of a majority of his teeth, a tendency to infections of the respiratory tract, and slight hemorrhoids for many years. During the last few years the patient had been conscious of a gradual slowing down of the mental processes, but this had failed to disturb his rather placid philosophy of life.

Laboratory Summary: The patient was a tall man, 12 per cent under weight and somewhat below his predicted lung volume. The basal rate was recorded as —15 per cent, a very moderate degree of hypofunction. With this was a low blood pressure and a definitely slow pulse. The urine showed both albumin and casts with a high residual nitrogen fraction. The sugar tolerance was normal, the blood chemistry normal, while the blood morphology showed a slight secondary anaemia with a substantially normal formula for the leucocyte count.

Radiogram: The teeth showed extensive periapical infection; the dorsal spine, hypertrophic arthritis; the skull was normal; the sella normal; optic canals unusually large but the bony margins were not eroded. The right frontal sinus was undeveloped.

Chest Examination: Dullness and some increased fremitus were observed. The condition was consistent with a healed tuberculosis.

Laryngological Examination: The examiner noted several doubtful teeth; infected but not apparently offending tonsils.

Neurological Examination: There was no direct evidence of organic nervous disease.

Ear Examination: No evidence of anatomical change.

Barany Test: Normal.

Audiogram: The hearing was fairly normal throughout the speech area coupled with a marked loss of hearing in the upper tones, suggestive of a luetic involvement of the 8th nerve.

Surgical Examination: Examination of the abdomen gave no evidence of tenderness or masses.

Gastro-Intestinal Study by Roentgenogram: Pericaecal adhesions were demonstrated.

Eye Examination: Showed marked cutting of the upper form and color fields, signifying pressure below the optic pathways, possibly in chiasm or possibly in the calcarine area. The blind spots were enlarged.

Spinal Fluid Examination: The results of this examination were negative except for a slightly high cell count.

Discussion: The laboratory picture here was not as sharply suggestive of thyroid failure as in some of the other illustrative cases. There was, however, a lowered basal rate which in a nervous individual would still be much above the truth. With this patient, however, there was a placidity arguing for probable authority in this test. The blood pressure and pulse were low; the kidneys gave some evidence of irritation. The urine volume was not suggestive. The high residual nitrogen and the normal sugar tolerance would be consistent with a thyroid failure. The supplementary tests, however, precluded such an interpretation of the laboratory findings.

CASE B-883—PULMONARY TUBERCULOSIS AND EPILEPSY SIMULATING HYPOTHYROIDISM. The patient's chief complaint was of convulsions from which he had suffered for the past five years. They were irregular in appearance, from twice in one day to once in two weeks, and lasted for periods varying from half a minute to ten minutes or more. The attacks also varied in severity, in the more severe of them there being frothing at the mouth, crying aloud and falling with loss of consciousness. There was apparently no aura and recovery was rapid after the passage of the seizure.

Family History: Not significant.

Past History: The boy reported only measles of the minor ailments of childhood and a broken left arm seven years previously. He reported infrequent headaches, an occasional nose-bleed, some nocturia, but the remaining history as given was practically without significant features.

Physical Examination: The patient was a well-developed, somewhat undernourished boy 13 years of age; the face and skin were pallid. The teeth were in good condition although they had received no attention. The lungs showed diminished tactile and vocal fremitus, but neither dulness nor rales were recorded. There was marked flat foot. The routine neurological findings were normal.

Laboratory Summary: The boy was 14 per cent underweight, with a substantially normal lung volume. The basal rate was 20 per cent below prediction, the blood pressure low, pulse normal, and there was a slightly febrile temperature. The urine volume was somewhat scanty and the excretion contained albumin. The nitrogen elimination indicated a wholly inadequate protein intake. The residual nitrogen fraction showed an upward tendency. The sugar tolerance was normal. The blood chemistry value was absolutely normal, but in view of his very low protein intake the nitrogen constituents were relatively high.

Chest Examination: The left lung gave evidences of a probable active tuberculosis, which indication was supported by the slight febrile temperature and other evidences.

Roentgenogram: Both lungs showed scattered, diffuse infiltration. The heart, mediastinum and skull were normal.

Laryngological Examination: Negative.

Neurological Examination: There were no objective neurological findings, the examiner regarding the history as suggestive of idiopathic epilepsy.

Eye Examination: Beyond yellowish discs and slightly enlarged blind spots, the results were normal.

Discussion: The laboratory picture here could have been interpreted in terms of thyroid failure had the other examinations and the history not indicated otherwise. The amyxedemic subject of thyroid failure is usually underweight. The boy was 20 per cent below his predicted basal rate with a slightly febrile temperature which could be interpreted as accounting for his pulse rate and in the correction of which a still lower basal value would be obtained. The boy's protein starvation is patently the cause of his low basal rate, however. The urine and blood picture were entirely consistent with the pseudonephritis of thyroid failure, while the lymphoid blood though not characteristic of this condition is to be expected in it. This case illustrates, in our opinion, the basic unwisdom of an effort to establish a diagnosis on the basal rate alone.

CASE S-1057—PULMONARY TUBERCULOSIS REFERRED FOR HYPERTHYROIDISM. The patient was a young man of 29 complaining of a lack of energy and ambition. He had been examined a month previously and told that this condition derived from thyroid disease and it was recommended that he receive treatment for this condition. The chief complaint had begun about two years previously and had been progressive during that interval.

Family History: The patient was a twin, his brother being in excellent health. The remaining family history was not relevant. The patient had been married for two years; his wife had borne one child, and had one miscarriage. The latter was ascribed to overwork.

Past History: The patient reported the minor ailments of childhood, scarlet fever, and a slight attack of pneumonia five years previously. He had been operated upon for a deviated septum a number of years earlier. He was subject to colds and a cough persisted after such an attack. Three years previously he had an attack of ptomaine poisoning and since that time he had been troubled with a mild gastritis and with flatulency.

Physical Examination: The patient was a well-developed but much undernourished young man of 29. The head showed a very prominent occipital protuberance suggesting a bony exostosis. The pupils showed a sluggish reaction to light and accommodation. The teeth gave evidence of much dental manipulation. The chest was flat, long and narrow, and there were marked supraclavicular depressions; rales were heard in both apices. The heart was normal; the skin dry and scaly; the knee jerks somewhat sluggish.

Laboratory Summary: The patient was 26 per cent underweight, lung volume slightly depressed. A satisfactory basal rate was 7 per cent above prediction; blood pressure was slightly low; pulse and temperature normal. The urine volume was somewhat large; remaining findings including the nitrogen partition measurements normal. The sugar tolerance was not determined. The blood chemistry was normal and the blood morphology presented a substantially normal picture.

Roentgenogram: The lungs showed increased prominence of the bronchial markings with peribronchial infiltration on both sides. A few small discrete calcifications were also noted.

Discussion: The interesting feature in this case is the normal basal rate coupled with the patient's definite emaciation. As will be noted in the table, the protein intake is ample. No part of the laboratory examination could be interpreted to support a diagnosis of thyroid failure, while the physical examination supported by the radiogram gave unmistakable evidence as to the cause of the patient's lassitude.

GROUP II. CASES SIMULATING SOME TYPE OF PITUITARY DISEASE

CASE S-1111—NORMAL INDIVIDUAL REFERRED FOR POSSIBLE HYPERPITUITARISM. The patient's chief complaint was of oversize, she being a young woman of 24 just under six feet in height. At about the age of 12 she began to grow very rapidly, and at the age of 14 developed a fatigability and fell behind in her school work from lack of ambition and inability to study. Infrequently she had had severe generalized headache which, however, lasted for only a few hours. She reported an excessive appetite, but stated that she maintained a fairly constant weight.

TABLE XIX

Simulation of Pituitary Disease

1. Normal referred for Hyperpituitarism.
2. Paget's Disease simulating Hyperpituitarism.
3. Cholecystitis and Duodenal Ulcer simulating Dyspituitarism.
4. Cardiac with Roentgenogram of sella suggesting Pituitary Tumor.
5. Syphilis simulating Dyspituitarism.
6. Cardiorenal disease simulating Hyperpituitarism.

	1	2	3	4	5	6
Case Number	S-1111	B-624	B-678	B-837	B-566	B-634
Sex	F	F	M	F	M	M
Age (yrs.)	24	39	41	57	61	59
Height (cm.)	179	160.5	178.5	159	167	173.5
Weight (kgm.)	72.6	61.4	62.9	81.8	76.2	73.4
Weight Deviation (%)	—4	+11	—20	+25	+20	+20
Lung Volume Deviation (%)	+1	—33	—17	—30	—31	—45
Basal Rate Deviation (%)	—7	+20	—15	—2	—19	+38
Blood Pressure (mm.)	112/74	130/80	102/58	192/108	110/78	264/120
Pulse Rate (per min.)	71	84	59	70	68	92
Temperature (deg.)	98.2	99.0	97.3	98.2	97.0	98.0
Alveolar CO_2 (mm.)	41	41	43	40	39	48
Urine Volume (cc.)	1400	490	740	790	890	650
Spec. Grav.	1.016	1.028	1.025	1.023	1.021	1.015
Albumin	0	+	0	0	0	+
Casts	0	0	0	0	0	+
Sugar	0	+	0	+	+	0
"Urobilinogen"	0	0	0	0	0	0
Total Nitrogen (gm.)	9.39	4.83	10.32	5.10	8.76	3.94
Residual Nitrogen (%)	5.3	16.1	10.5	5.3	5.5	24.1
P. S. P. (2 hours) (%)	7.5	46	52	54	47	0(?)
Galactose Tolerance						
Normal (gm.)	..	40	30	30	30	30
Observed (gm.)	..	10	10	30	5	5
Deviation (%)	..	—75	—67	±0	—83	—83
Blood						
N. P. Nitrogen (mgm.)	33	30	30	35	43	47
Uric Acid (mgm.)	3.0	4.7	3.1	3.2	3.4	5.4
Sugar (mgm.)	96	105	87	95	100	105
Haemoglobin (%)	85	95	80	85	90	55
Erythrocytes (10^6)	4.28	5.40	4.67	4.67	4.52	3.09
Color Index	1.00	0.88	0.86	0.91	1.00	0.89
Leukocytes (10^3)	5.1	7.6	8.8	7.6	7.8	7.2
Neutrophiles (%)	45	53	55	68	61	80
Lymphocytes (%)	50	40	36	21	35	9
Eosinophiles (%)	1	2	2	2	1	2
Endothelials (%)	4	4	7	9	3	9
Misc. (%)	0	1	0	0	0	0
Wassermann	0	0	0	0	+	0
Spinal Fluid	0	0	—	—	—	—

Family History: The patient's father was six feet in height. She had a sister 5 ft. 8 in. tall. The mother and a brother were of usual size.

Past History: The patient reported the usual ailments of childhood, diphtheria, and an appendectomy at the age of six. Beyond the points noted above the remaining history was entirely normal, including that of the catamenia.

Physical Examination: The patient was a very well-developed and well-nourished young woman with an exceptionally good musculature. There was a slight pilosity on the upper lip, and hypertrichosis of the extremities. The teeth were apparently somewhat soft. The neck was large and muscular, the thyroid not palpable. The breasts were small but entirely normal. Remaining findings, with the exception of hyperactive knee jerks, were not significant.

Laboratory Summary: The patient was 4 per cent underweight; the basal rate 7 per cent below prediction. The urine was entirely normal. Blood chemistry was normal. Blood examination showed a slightly low value for the erythrocytes with a relative lymphocytosis.

Roentgenogram: The skull was normal; the sella of normal size and configuration.

Eye Examination: The blind spots were slightly enlarged.

Discussion: The patient's physical habitus was strongly suggestive of pituitary disease with overactivity of the anterior lobe. The laboratory examination completely failed to confirm this indication. It is, of course, possible that the patient had had an earlier period of pituitary overactivity, but if such had been the case it had certainly been followed by spontaneous correction and at the time of the examination there was lacking any of the conventional evidences which experience has associated with disturbed pituitary function. The establishment of catamenia at the normal age, and its normal course thereafter, are arguments against the existence of any earlier significant disturbance of pituitary function. The girl was in a state of vigorous health, actively engaged in her profession. A study of this patient at some time in the future might be interesting from the standpoint of the present normal findings, but at present she illustrates the fallacy of making a diagnosis of an endocrinopathy from the history and physical examination alone. This case with those preceding it, prove the interdependence of complete clinical and laboratory examinations in the study of endocrine disturbances.

CASE B-624—PAGET'S DISEASE SIMULATING HYPERTHYROIDISM. The patient's chief complaint was of pain in the right leg which she had first noticed some eight years previously. There was apparent improvement during the warm weather in the summer and an exacerbation in the winter, which in the last few years had become seriously crippling. Bandaging and rest had failed to bring relief. At the time of her periods of exacerbation there was usually intense headache and arthritic pains in the shoulders. During the previous year the attacks had become more frequent and of longer duration. A few months prior to admission a bony tumor had been removed from the right tibia. There had been a possible slight improvement as a result of this surgical intervention.

Family History: There was a definite history of longevity, the maternal grandfather having reached the age of 109.

Past History: In addition to the usual ailments of childhood the patient reported tonsillitis and four attacks of pneumonia. She had influenza at the time of the epidemic and had considerable pleurisy at this time with recurrences of the latter every winter. She had had repeated attacks of malaria prior to her attacks of influenza. She complained further of severe periodic headaches noted above which were accompanied by vertigo, but which would ultimately be relieved by medication. During the attacks of pain there was a lowered aural acuity. She was subject to frequent head colds and had chronic catarrh. Had lost numerous teeth in connection with her several pregnancies. She complained of dyspnoea, palpitation, had had night sweats but not recently, and an irritating but non-productive cough. She had occasional attacks of nausea in the morning. The menses were established at 12 and after a few periods amenorrhoea developed and persisted up to the age of 16, when the menses recurred spontaneously, the periods being of normal interval and amount. She had been married for 18 years and had borne four children without miscarriage. She reported herself as nervous, emotional and with a tendency to depression. A surprise would produce tingling sensations over the entire body and there was an intermittent numbness of the lower extremities with failure to apprehend sharp or dull point contacts.

Physical Examination: The patient was a well-developed, well-nourished woman of 40. There was a slight nasal obstruction, a coarse tremor of the tongue, many teeth missing, and the tonsils were enlarged. A blowing systolic murmur was reported and occasionally a diastolic murmur as well. The right leg showed residua of her earlier operation. The knee jerks were exaggerated, and on the right side she exhibited a crossed reflex of the adductor and flexor group of the left thigh.

Laboratory Summary: The patient was 11 per cent above her predicted weight and significantly below her predicted lung volume. The basal rate was reported as 20 per cent above prediction, and this finding was confirmed by later observations. The temperature was slightly high, the remaining physical findings, normal. The urine was scanty in volume and contained both albumin and sugar. The total nitrogen indicated an inadequate protein intake. The residual nitrogen fraction was much above the normal. The sugar tolerance showed a marked depression, confirming the record of glycosuria. The blood uric acid was distinctly above the normal. The blood morphology showed a lymphocytosis but was otherwise normal.

A report from the institution where the operation had been performed was as follows:

"*X-Ray Report:* There is an area extending from the mid-portion one inch below the lower end of the tibia which exhibits marked thickening of the cortex. The medulla is obscured in several areas while others of lessened density are observed in other portions." Later reports showed the condition apparently extending and some time thereafter an operation was performed exposing the point of greatest anterior convexity. The cortex of the tibia was found to be thick and dense, periosteum thin and adherent; irregular calcified areas were observed in the marrow cavity which when broken down formed a rough thin wall of the cavity. The bone tissue was soft as from a chronic degenerative process. No pus was obtained.

Neurological Examination: A positive Romberg test was reported, pupillary reflexes to light were stiff, the coördination of the upper extremities was very poor and there was a coarse tremor.

Spinal Fluid: Examination was entirely negative.

Orthoredic Examination: The leg condition was described and on the basis of the history, pathological findings at the time of operation, and general evidences, it was suggested that the condition was similar to that described by Henderson, who named it an osteoscleros-ing osteitis.

Roentgenogram: The chest showed increased density over the lower half of both lungs; the skull showed thickening of the occipital and parietal bones with recalcification and sponge-like markings of the lateral wall. The pelvis, hips and lumbar spine showed calcium deposits of the bones with some increase in their transverse diameter. Similar changes were remarked in the lower half of the right humerus.

Ear Examination: There were some middle ear changes suggestive of early chronic catarrh.

Barany: Normal.

Audiogram: There was definite loss of hearing in both ears.

Eye Examination: The sluggish pupillary reflexes were not confirmed. Yellow discs, much enlarged blind spots, and marked symmetrical contraction of the form and color fields were noted.

Discussion: This patient had Paget's disease, with thickening of the skull, and probably some increase in intracranial pressure. Her scanty urine was not suggestive of pituitary disease. There was a high residual nitrogen, increased basal rate, high blood uric acid, much lowered sugar tolerance, and the findings of the eye examination were all suggestive of overactive pituitary. It is perfectly true that intracranial pressure could have produced some disturbance of pituitary function; it would, however, be secondary to the presenting condition. There was seemingly some pulmonary involvement and one of us (A. W. R.) has already noted marked symmetrical contraction of the form and color fields in pulmonary tuberculosis. The intracranial pressure could produce a lowered sugar tolerance through interference with the central nervous system without involving the pituitary. It is to be noted that the blood sugar was entirely normal. The slightly increased basal rate was substantiated by two concordant measurements which were reported as satisfactory. In both of these, however, the pulse was somewhat rapid and at a level considerably superior to the daily pulse rate as shown by the nurse's record. While we feel that there may have been some secondary pituitary influence in this case, the bulk of the supporting evidences are susceptible of a non-endocrine explanation. The case is presented as an interesting simulation of pituitary disease which could have been misleading in the primary diagnosis. A later case, not recorded in this group, presenting Paget's disease in a much more advanced state, showed a like depression of the sugar tolerance and an entirely normal basal rate. This latter patient was much more stable nervously, and the basal rate probably more truly representative. It is interesting to note how purely extraneous factors may exercise an apparently constant influence on such a measurement as the basal rate. Elsewhere in these papers comment has been made on a case of paralysis agitans with marked tremor which week after week showed a level which fell between the narrow limits of +60 per cent and +65 per cent. The true rate was either normal or possibly a little below, as was shown by certain supplementary measurements which need not be discussed here.

CASE B-678—CHOLECYSTITIS AND DUODENAL ULCER SIMULATING PITUITARY DYSFUNCTION. The patient's chief complaint was of flatulency and pain in the stomach associated with an intermitten diarrhoea. Four years previously he had a so-called nervous breakdown as the result of a strained domestic situation. On his recovery a few months later he began to experience pain in the lower left quadrant. He was examined and a varicocele was found which was operated, and this relieved the pain in the left inguinal region. A few weeks later, however, he developed pain in the left lumbar, iliac, hypochondriac, and epigastric regions. The attacks of pain were intermittent but occurred periodically. At times food would relieve him, at others it was ineffective. Rest seemed to bring the greatest benefit. For the past three years he had had diarrhoea practically every summer. He was troubled with hemorrhoids; he emphasized the fact that there was no pain on the right side. He was of a high-strung nature, very nervous, and greatly disturbed if he were alone. He gave a long list of foods, mostly indigestible in character and with a high fat content, which he was unable to tolerate.

Family History: Not relevant. The patient had been married for a number of years but had divorced his wife at about the time of the onset of his present illness. The marriage had been infertile. The loss of his wife had affected him deeply and the unhappiness resulting from it was a very definite factor in the general picture.

Past History: He had no recollection of any of the minor ailments of childhood but had had an attack of melena at the age of twelve and many recurrences up to five years previously. He had had a number of teeth removed; complained of urinary frequency and urgency, during his periods of nervousness. The remaining history as given by him was not significant. As a matter of fact his physician had referred him for this study because of several transitory attacks of aphasia.

Physical Examination: The patient was a tall, thin man, fairly well developed and nourished, 41 years of age. There was some loss of hair from the vertex, a suggested exophthalmos was no more than a family peculiarity, many teeth were missing, there was a doubtful thyroid enlargement. The breath had an odor which suggested to the examiner that of known gastric ulcer cases. The abdomen was apparently normal. There was a slight supraclavicular adenopathy, a contraction of the left side of the scrotum which was a post-operative condition, and a negative routine neurological examination.

Laboratory Summary: The patient was 20 per cent underweight and somewhat below his normal lung capacity. A basal rate of —15 per cent was recorded with low blood pressure and a downward tendency of both pulse and temperature. The urine was somewhat scanty but otherwise normal. The residual nitrogen fraction was high. The sugar tolerance was depressed much below the normal level. The blood chemistry was normal. The blood morphology showed a slightly low haemoglobin value and a lymphoid blood.

Surgical Examination: Negative. In the examiner's opinion a peptic ulcer was probable.

Radiograms of Gastro-Intestinal Tract: The duodenum showed a niche on the anterior border suggesting a duodenal ulcer.

Graham Test: The test was negative, but was performed by the oral route.

Stool Examination: The presence of blood was demonstrated.

Eye Examination: The pupils showed moderately active reactions and the fundi gave some evidence of vascular hypertension. The blind spots were enlarged and there was some contraction of the form and color fields.

Discussion: Were it not for the patent gastro-intestinal condition it would be possible in this case to consider a pituitary dysfunction as present. As it is, the lowered basal rate derives from the patient's under nutrition, the lowered sugar tolerance from the liver dysfunction which was offered in the preliminary opinion and later verified elsewhere, while the eye findings were also presumably referable to this latter cause.

CASE B-837—CARDIAC DISEASE WITH A RADIOGRAM OF THE SELLA SUGGESTING PITUITARY TUMOR. The patient's chief complain was of severe headache localized in the vertex and the occipital portions of the head. She also suffered from high blood pressure. Seven years previously, at the time of the menopause, the patient being 50 years of age, she had developed very severe headaches, with which there was some associated vertigo. The hypertensive condition showed on examination and she was placed under treatment for this with a gradual improvement both in the blood pressure and in the headaches. Some eight months previously, however, there had been a recurrence of the condition and the physician called at that time recommended glandular therapy. Further questioning elicited the fact that five years previously she had had some trouble with her feet and her physician at that time recommended weight reduction and gave her thyroid therapy to produce this end. At other times she had been given other glandular preparations, although she was not certain of the character of them. At the time of admission she had not been receiving any endocrine medication for several months.

Family History: Both mother and father had died of apoplexy, and this fact intensified the patient's worry over her own high blood pressure. She had been married for 29 years without conceiving although contraception had not been practiced.

Past History: She reported minor ailments in childhood, pleurisy with effusion at the age of 14, abscessed tonsils at 15, and influenza at the time of the epidemic. Many years previously a herniotomy had been performed. At the time of admission she complained of a constant dull feeling of fullness in the head punctuated by very severe headaches as noted above. There had been a considerable loss of hair. She had two severe nose-bleeds five years previously; was subject to hay fever and apparently sensitized to a large number of pollens; she had had earlier sensitivity to strawberries which had corrected itself spontaneously. She had had three acute digestive attacks in the past three years characterized by nausea and vomiting. She had never been jaundiced but had had clay-colored stools after these attacks. She was somewhat constipated. Over 20 years earlier she had voided a small renal calculus after an illness of three days. There had been no recurrence. Menstrual history showed an early onset, large periods with shortened interval, but from 1906 on until an uneventful menopause seven years previously, the function had been entirely normal. She regarded herself as nervous and emotionally unstable. She complained somewhat of vertigo.

Physical Examination: The patient was a well developed, obese woman 57 years of age; the hair was somewhat thin, peripheral vessels showed some degree of sclerosis, blood pressure was distinctly high, abdomen entirely normal, knee jerks hyperactive and the remaining routine neurological findings normal.

Laboratory Summary: The patient was recorded as 25 per cent overweight but with her high sitting height index this figure was actually too low. There was distinct though not severe loss of lung capacity. The basal rate was —2 per cent, blood pressure at a definitely hypertensive level, pulse and temperature normal. The urine volume was somewhat scanty; a slight trace of sugar was reported in the first specimen but could not be confirmed in subsequent examination. The protein intake was below a maintenance level; the partition formula was normal. The sugar tolerance was normal, blood chemistry normal, while the blood morphology showed an entirely normal picture.

Roentgenograms: The chest examination was negative. The skull showed a bony thickening of the inner table and there was apparently some erosion of the posterior clinoid process. The sinuses were negative. The plates of a gastro-intestinal series were negative. The Graham test showed a normal organ.

Laryngological Examination: The patient had infected tonsils; the remaining examination was negative.

Cardiogram: Showed a left axis deviation consistent with, but not determining, cardiac enlargement. The remaining findings were entirely normal.

Heart Examination: There was a visible impulse in the suprasternal notch; definite angulation of the carotid arteries could not be detected on palpation; the heart was not enlarged; there was a soft systolic murmur with the first sound over the base and transmitted slightly toward the neck. The blood pressure was distinctly hypertensive. The examiner's opinion was of a chronic arterial hypertension without much change in the heart or the arteries.

Orthopedic Examination: The patient presented an obesity with a compensating lumbar lordosis. The posture was poor. Some of the joints of the hands showed a slight limitation in flexion due to a symptomless arthritis.

Eye Examination: The fundi gave evidence of a moderate degree of vascular sclerosis and there was slight blind spot enlargement.

Neurological Examination: No evidence of disease of the nervous system.

Special Blood Examination: The calcium, phosphorous and fibrin content was entirely normal.

Discussion: Stereoscopic plates of the sella were requested but it was not possible to secure them. In our experience we have had several reports of clinoid erosion which could not be substantiated at autopsy. In the present instance there was not one single finding suggestive of disturbed pituitary function. The normal basal rate would be as inconsistent with anterior lobe disturbance as would the normal sugar tolerance with that of the posterior. The single report of a trace of sugar in the urine could not be verified. With the condition of hypertension such as that presented by the patient such a glycosuria might well be referable to an injury to the central nervous system associated with arteriosclerosis. While the patient was obese, this fact alone would be a most uncertain basis for a pituitary diagnosis. It is, of course, always possible that there could be tumor growth of the pituitary without change of function. Such a condition in the thyroid is frequently remarked in endemic goiters. In our experience, however, cases presenting proven pituitary tumor have always given extensive and unmistakable evidences of disturbed pituitary function. In the present instance, lacking every evidence but that of a flat x-ray plate, we felt warranted in eliminating any pituitary element from the picture. The subsequent history of the case substantiated this conclusion. In view of the strictly non-endocrine character of this patient her earlier history of endocrine medication is not uninteresting.

CASE B-566—SYPHILIS SIMULATING PITUITARY DYSFUNCTION. The patient's chief complaint was of a marked fatigability complicated by pain in the left arm and shoulder, beneath the left breast, and at times in the left knee. This condition had obtained for the past six years. Over substantially the same period he had more or less digestive disturbance and had been growing progressively more deaf. While active physically and strong muscularly, he had become more and more fatigable and for the past two years, as he phrased it, he had been working "on his nerve."

Family History: In the main not informative. Patient was married at the age of 21 and was divorced by his wife after 32 years of married life. During that period she bore three children without miscarriage. Four years previously he had married again. The second wife had never conceived.

Past History: He reported a few minor ailments, typhoid at 30, and diphtheria 10 years ago. He had always lived an active life and had worked very hard. He complained of a twiching of the right eyelid when tired; a gradual loss of hearing, more marked on the left side; a slight productive cough some years previously; a foul taste in the mouth on awakening; flatulency, and a variety of gastric disturbances which he could not describe clearly. At times he had a dull pain in the region of McBurney's point. He had had a Neisserian infection as a young man but denied lues. For a good many years he had had a left intercostal neuralgia and latterly some slight general swelling and stiffness in the joints. Also when fatigued there was a dull ache in the region of the sacrum.

Physical Examination: The patient was a well-developed, overnourished man of 61. The hair on the head was thin, the eyes apparently normal; there was a definite loss in aural acuity, marked varicoses on the under surface of the tongue. There was apparently a slight cardiac enlargement; the sounds were indistinct, but no murmurs were heard; the blood pressure was low. The abdomen was somewhat distended and there was apparently some flatness to percussion on the sides. There was moderate tenderness on deep palpation over McBurney's point and also some in the epigastric region. There was tenderness over the left shoulder at the acromio-clavicular junction, over the deltoid, and in the axilla; also on the medial aspect of the left knee. The hands showed some joint enlargement. Routine neurological examination was negative.

Laboratory Summary: The patient was 20 per cent overweight with definite loss of lung volume. The basal rate was recorded as —19 per cent; the blood pressure and temperature were low. The urine volume was a low normal; sugar was reported in all specimens. Residual nitrogen was normal, sugar tolerance greatly decreased. The non-protein nitrogen in the blood was above the normal; uric acid and sugar were normal. The blood morphology showed a slight lymphocytosis. The Wassermann and Kahn tests were repeatedly positive.

Ear Examination: Normal.

Barany: Normal.

Stool Examination: Negative.

Cardiogram: Normal.

Heart Examination: Beyond indistinct heart sounds, the heart was entirely normal.

Neurological Examination: The pupils showed sluggish reactions and there was an ill-defined tenderness over the nerves of the brachial plexus.

Orthopedic Examination: The case suggested sub-deltoid and sub-acromial bursitis. The left knee showed a slight degree of hypertrophic arthritis. There was also a suggestion of some abnormality of the semi-lunar cartilage.

Abdominal Examination: The findings reported in the physical examination were not confirmed. No surgical condition was demonstrated in the abdomen.

Gastro-Intestinal Radiograms: The stomach, duodenum, and bowel were normal. The appendix was diseased.

Audiogram: The curve showed that sharp loss in the upper tones which we regard as somewhat characteristic of syphilis.

Eye Examination: The pupillary reactions were sluggish, the remaining examination negative.

Discussion: While several independent disease conditions were demonstrated by this examination, those findings suggestive of a pituitary dysfunction would have been accounted for by the demonstrated syphilis. The opinion as to the underlying condition hinges about the serological examinations, and these gave positive responses on repeated testing.

CASE B-634—CARDIO-RENAL DISEASE SIMULATING HYPERFUNCTION OF THE PITUITARY. The patient's chief complain was of marked distress and shortness of breath. This condition had appeared in recurrent attacks of several weeks' duration, the first of which was remarked three years ago. During the lapse of time they had occurred more frequently and in the past few months the dyspnoea had been practically constant. He had acute attacks of shortness of breath which would wake him up at night. Treatment with nitro-glycerine had been non-effective. There was also a progressive weakness of the skeletal muscles without abrupt loss of control or paralysis.

Family History: Negative.

Past History: The patient reported the minor ailments of childhood and a hemorrhage of the stomach at the age of 27. He complained of occasional headaches, some vertigo, a non-productive cough, an occasional night sweat which he ascribed to nervousness, and a normal gastro-intestinal history. He stated that the urine stream was slow in starting and subject to interruption. There was some dysuria of varying degrees. The prostate had been examined a year or two earlier and pronounced normal. He had gonorrhea twice in young manhood and syphilis at about the same time. Was treated for the latter with apparent success, as numerous Wassermann tests have always been negative. He complained of intermittent pain in various joints which was never accompanied by swelling. He had at one time been very obese but had gradually lost nearly 100 lbs. during the past 20 years.

Physical Examination: The patient was a well-developed, overnourished man of 59 years of age. There were numerous small, unpigmented papillomata on the face. The pupillary reactions were somewhat sluggish. The nose suggested rhinophyma. The expirations were prolonged and marked friction rubs were heard throughout the chest. There was a slight dulness in the upper chest, tactile and vocal fremitus increased in the right apex, and many dry coarse rales were heard throughout the chest. The heart was enlarged to percussion and there was a systolic murmur at the apex. The abdomen was asymmertical, the left abdomen being somewhat enlarged. There was some flatness on percussion; the liver was apparently enlarged. A cough impulse was felt in the left inguinal region. There was some edema of ankles and feet. The routine neurological examination was negative.

Laboratory Summary: The patient was 20 per cent overweight and definitely below his predicted lung volume. The basal rate was reported as 38 per cent above prediction. There was a marked degree of hypertension with somewhat rapid pulse. The urine volume was somewhat low; albumin, granular and renal cell casts were observed. The protein intake was entirely inadequate; the residual nitrogen fraction was definitely high. Three repeated sulphonephthalein tests failed to return enough of the dye to measure quantitatively. The sugar tolerance was greatly diminished; both non-protein and uric acid were much above the normal; the blood morphology showed a marked secondary anaemia and a predominance of the neutrophilic elements.

Roentgenograms: The skull was normal. A measured heart plate showed definite cardiac enlargement. There was a diffuse mottled infiltration of both lungs, more marked at the bases.

Cardiogram: There was a left axis deviation consistent with cardiac enlargement. The initial ventricular complex was of maximum duration and, together with the inversion of the "T" waves, indicated a probable impairment of the ventricular myocardium.

Discussion: The patient was an advanced case of cardio-renal disease with the possible complication of a neuro-syphilis which it was felt wiser not to investigate by spinal puncture. The increased basal rate could derive from the patient's breathing and the inability to secure a truly basal reading. The high residual nitrogen of the urine is no more than an evidence of this toxic state. The high blood uric acid is robbed of its endocrine significance by the high values of the other nitrogenous constituents. The low sugar tolerance is referable either to the arterio-sclerosis, the possible neuro-syphilis, or a possible liver condition suggested by the report of hepatic enlargement. In the same way other suggestions of possible endocrine disorder are directly traceable to the better established non-endocrine conditions which presented. This laboratory picture is a simulation of a hyperpituitary state for which supporting evidence is entirely lacking.

GROUP III. CONDITIONS FREQUENTLY ASCRIBED TO ENDCRINE CAUSES

CASE S-1712—DELAYED ONSET OF MENSTRUATION DUE TO PULMONARY TUBERCULOSIS. The patient's chief complaint was of having failed to establish the menses at the age of 18. She had been under medication for this condition for some time and complained of periodic attacks of pain, occurring at intervals of four weeks and lasting for one day. These pains had developed since beginning her medication. She also complained of marked fatigability.

Family History: Negative.

Past History: In addition to the minor ailments of childhood the patient had a severe attack of influenza at the time of the epidemic and had been consistently susceptible to respiratory infections. She reported the loss of 20 lbs. in the past 2 years. She had had frontal headaches, but these had been corrected by proper glasses. She complained further of indigestion after eating fried foods. The remaining history as given was entirely irrelevant.

Physical Examination: The patient was a well-developed and well-nourished young woman nearly 19 years of age. There was some tonsillar enlargement, rapid pulse rate, a loud systolic blowing murmur most marked at the apex and transmitted to axilla and sternum.

The remaining findings were normal. It should be remarked in passing that an incompetent examiner failed to note the definite evidences of pulmonary disease.

Laboratory Summary: The patient was 6 per cent overweight, but as the sitting height index was low this figure is misleading and she was actually somewhat underweight. The lung volume was much below the predicted level. The basal rate was normal. She had rapid pulse, low blood pressure and slightly sub-normal temperature. Be-

TABLE XX

Conditions Ascribed to an Endocrine Etiology

1. Delayed menstrual onset due to pulmonary tuberculosis.
2. Obese Normal Giant simulating Hypopituitarism.
3. Dwarfism with congenital Syphilis.
4. Chondrodysplasia with syphilis (congenital).
5. Achondroplastic dwarf with rickets and congenital malformation of skull and spine producing a lesion of the central nervous system.
6. Progressive muscular dystrophy.
7. Diabetes insipidus.

	1	2	3	4	5	6	7
Case Number	S-1712	S-131	B-356	B-123	B-663	B-251	B-839
Sex	F	M	F	M	M	F	M
Age (yrs.)	18	52	16	24	7	22	5
Height (cm.)	165.0	193.0	143.5	157.5	99.0	151.0	103.0
Weight (kgm.)	53.0	145.0	40.0	52.4	19.3	40.5	15.5
Weight Deviation (%)	+6	+67	—7	—12	—15	—1	—10
Lung Vol. Deviation (%)	—44	—23	—11	—8	—24	—20	—16
Basal Rate Deviation (%)	—1	+6	—10	+7	*+22	—3	+7
Blood Pressure (mm.)	106/64	156/78	94/58	92/58	88/68	118/84	95/52
Pulse Rate (per min.)	106	76	72	71	100	81	90
Temperature (deg.)	97.4	97.8	98.6	98.8	99.2	98.8	97.8
Alveolar CO_2 (mm.)	41	52	**33**	36	42	**29**	35
Urine Volume (cc.)	780	1540	1150	920	330	460	960
Spec. Grav.	1.021	1.021	1.021	1.027	1.030	1.021	1.013
Albumin	0	0	+	0	0	+	+
Casts	0	0	+	0	0	0	0
Sugar	0	0	0	+	+	+	0
"Urobilinogen"	0	0	0	0	0	0	0
Total Nitrogen (gm.)	8.55	11.46	7.75	15.38	5.12	4.70	5.38
Residual Nitrogen (%)	15.3	8.7	8.1	3.0	21.6	6.7	7.9
P. S. P. (2 hours) (%)	54	61	64	48	53	57	51
Galactose Tolerance							
Normal (gm.)	..	..	40	30	30	40	30
Observed (gm.)	..	..	20	40	5	40	20
Deviation (%)	..	..	—50	+33	—83	± 0	—33
Blood							
N. P. Nitrogen (mgm.)	30	35	33	40	25	31	30
Uric Acid (mgm.)	4.2	4.5	3.0	4.4	2.8	2.5	2.8
Sugar (mgm.)	95	109	96	83	80	81	*117
Haemoglobin (%)	90	100	100	100	80	75	85
Erythrocytes (10^6)	4.98	5.67	5.80	5.55	4.26	4.16	4.87
Color Index	0.90	0.88	0.86	0.90	0.94	0.90	0.87
Leukocytes (10^3)	6.9	7.65	5.40	7.70	10.2	7.7	10.0
Neutrophiles (%)	56	40	54	68	42	62	39
Lymphocytes (%)	35	43	39	24	47	29	37
Eosinophiles (%)	2	6	4	0	6	5	6
Endothelials (%)	6	9	3	7	5	4	18
Misc (%)	1	2	0	1	0	0	0
Wassermann	0	0	0	+	0	0	0
Spinal Fluid	—	—	—	—	—	—	—

*Too high emotional reaction.

yond a slightly low volume and a definitely high residual nitrogen, the urine picture was substantially normal. The sugar tolerance was not determined. The blood uric acid was high. The blood was lymphoid in type.

Pelvic Examination: Entirely negative.

Laryngological Examination: Tonsils were buried, cryptic and infected. There was some muco-purulent material in both nares.

Radiogram: Both lungs were hazy. There was increased density of the whole of the right lung, fine linear markings of fibrosis and scattered mottled areas.

Cardiogram: This indicated a normal mechanism at an accelerated rate.

Eye Examination: Slight blind spot enlargement.

Discussion: The medicine used in this case was said to be a preparation of wormwood. The patient had a definite pulmonary tuberculosis, confirmed by later examination. There was no evidence in the laboratory examination of any endocrinopathy. The delayed onset of the menses must be ascribed to the asthenia deriving from the pulmonary condition. The administration of an endocrine preparation containing thyroid extract to a patient with active tuberculosis is, of course, definitely contraindicated, yet such therapy is recommended as a "therapeutic test" in amenorrhoea by certain contributors to "endocrine" literature.

CASE S-131—AN OBESE, NORMAL GIANT, SIMULATING PITUITARY DISEASE. The patient had no chief complaint other than obesity which dated back to early childhood and which had always been correctible by dietary measures.

Family History: The family history showed an unusual degree of longevity in the previous generations; the whole family was composed of large, heavy individuals. The patient had been married for 10 years, but the union was infertile.

Past History: The patient reported only measles in childhood, a peritonsillar abscess 12 years previously, and a brief attack of arthritis 6 years earlier. The remaining points were a tendency to constipation, occasional distress after eating and rarely, an attack of lumbar pain. The whole history was in the main one of vigorous health.

Physical Examination: The patient was a man of large stature weighing over 300 lbs. Development was excellent and there was marked physical strength and muscular development. The pupillary reactions were slightly slow; several teeth were missing but the remainder in excellent condition. The blood pressure was slightly high. Knee jerks were somewhat sluggish. Remaining examination was not significant.

Laboratory Summary: The volume of urine was normal, and the material itself free from abnormality. The patient was 67 per cent above his predicted weight and somewhat below his predicted lung volume. The basal rate was +6 per cent; the blood pressure, as noted, slightly high; pulse and temperature, normal. The sugar tolerance was not determined. Blood chemistry was normal except for a high uric acid. Blood morphology was normal except for lymphocytosis and 6 per cent eosinophilia.

Neurological Examination: Entirely negative.

Radiographic Examination: The skull, sella, and sinuses were normal.

Cardiogram: Normal.

Audiogram: Normal.

Laryngological Examination: Negative.

Eye Examination: The fundi showed slight vascular sclerosis and there was a very slight blind spot enlargement.

Discussion: On outward evidences this patient would have been diagnosed as a case of pituitary disease and the obesity considered to be probably of that origin. The only two points which could support such a diagnosis were the high blood uric acid and the eosinophilia; in addition there was the general though not specific indication of a lymphoid blood. That there may have been an earlier pituitary condition is certainly possible, but at the time of this study there were no valid evidences to support a diagnosis of current pituitary disease. Subsequently by moderate dietary restriction alone the patient took off some 60 lbs. in weight. The case is presented as records show that many subjects of obesity who presented far less convincing outward evidence of pituitary disease have been given pituitary medication for its correction.

CASE B-356—DWARFISM WITH CONGENITAL SYPHILIS. The patient's chief complaint was of small stature, she being but four feet nine inches tall at the age of 16.

Family History: The child was illegitimate; the father was unknown and the antecedents of the mother not a matter of record.

Past History: The patient reported none of the minor ailments of childhood but had a history of frequent sore throats, which had recently been somewhat benefited by a tonsil operation. She had had severe left frontal headaches all her life, at times accompanied by nausea and by occasional vomiting. The eyes were astigmatic and not strong. She complained of occasional vertigo and had had several fainting attacks after moderate exercise. She complained also of tinnitus which usually accompanied her vertigo. She had established the catamenia some six months earlier and the periods have occurred at intervals of from two to three weeks. They were apparently normal in duration and amount. There had been no increase in her weight or height for eighteen months prior to admission.

Physical Examination: The child was well developed, if allowance be made for her small stature. She was in an excellent state of nutritional equilibrium. The hair was abundant and coarse, with both light and dark strands and a few streaks of gray; a rather heavy growth in the axillae and on the pubis, the latter being normal in distribution. The pupillary reactions were very sluggish. The teeth were small and very closely set. The breasts showed inverted nipples. The heart and lungs were apparently normal. The routine neurological findings as reported were apparently normal.

Laboratory Summary: The child was 7 per cent below her predicted weight, but as the sitting height index was somewhat high, she was actually somewhat nearer conventional standard. The lung volume was but slightly increased. The basal rate was —10 per cent, this being the lowest value of several concordant determinations. The blood pressure was low. The value obtained for alveolar carbon dioxide was low, but this was probably due to the difficulty in obtaining a truly representative sample. The urine volume was normal; both albumin and casts were reported. The protein intake was adequate but not liberal. The residual nitrogen fraction was within normal limits. The sugar tolerance was half the normal. The blood chemistry was normal. The blood showed a lymphoid trend with a 4 per cent eosinophilia.

Neurological Examination: Negative.

Radiographic Examination: The skull was normal, as was the heart; there was some increased density over the pulmonary apices.

Eye Examination: The eyes showed the pepper and salt pigmentation of the retinae characteristic of congenital syphilis. As already noted, the pupillary reactions were sluggish; there was some loss of visual acuity. Both form and color fields were symmetrically contracted in moderate degree and the blind spots were definitely enlarged.

Discussion: There was nothing in this case to indicate any endocrine cause of her dwarfism. The social history, lowered sugar tolerance, and the very characteristic eye findings were felt to indicate the probable cause of the patient's arrest. We were unable to secure permission to perform a lumbar puncture. The Wassermann on the blood was negative, which fact would not invalidate the conclusion reached above. There was a report which we could not confirm that the mother was known to have been syphilitic. What was known of her social history, however, made the report a very credible one.

CASE B-123—CHONDRODYSPLASIA WITH CONGENITAL SYPHILIS. The patient was a man of 24 presenting as his chief complaint an inability to pronate the right forearm. There were numerous exostoses on all of the long bones. The difficulty with the forearm apparently originated after a fall in which he injured it. The generalized exostoses, so far as he knew, went back to early childhood.

Family History: At the time of his admission he reported only the death of his mother from tuberculosis, and an arthritic condition in his father. Later when the study was well under way in response to indirect questioning he added that the father was a man of very loose sexual life and that to his knowledge he had been under treatment for veneral disease.

Past History: The patient had apparently escaped all of the minor ailments of childhood, scarlet fever at the age of 9, and the removal of a wen some years earlier being the only two incidents noted. He denied venereal disease by name and symptom. His remaining history was substantially irrelevant.

Physical Examination: The patient showed fair development and nourishment. The teeth gave evidence of much dental attention. There was a slight enlargement of the thyroid; the ribs were prominent and beaded; the heart was apparently normal; the liver was slightly enlarged but was not tender, and there was no tenderness over the gall bladder region. There was limited pronation of the right forearm, but no limitation of motion. Marked exostoses could be demonstrated at both the upper and lower ends of all of the long bones. This condition was most pronounced at the lower ends of the femurs and tibiae. Overriding toes presented on both feet. The skin showed a generalized acne. The remaining findings were not remarkable.

Laboratory Summary: The patient was 12 per cent below his predicted weight, but as he had the very high sitting height index (0.555), the predicted weight was disproportionately high. The lung volume was practically normal. The basal rate showed the normal value of +7 per cent, the blood pressure was definitely low. Alveolar carbon dioxide was a low normal. The urine volume was normal, elimination good; a trace of sugar was recorded. The protein intake was ample—the patient spoke of himself as a very large meat eater. The partition formula was normal. His sugar tolerance was reported as slightly above the normal. This finding was regarded as questionable, since he eliminated nearly two grams with a test meal of 40. The patient was not entirely coöperative and it was impossible to verify this finding by repetition. On the basis, however, of many thousands of these tests, it was felt probable that his sugar tolerance is either normal or even possibly diminished. The record, however, is given as it stands. It will be noted there was a slight glycosuria. The blood uric acid was above the normal but the non-protein nitrogen was at a similar high level. The blood morphology showed a substantially normal picture. The Wassermann test gave a strongly positive response in several independent observations.

Eye Examination: The pupillary reactions were sluggish. The form fields were normal, the color fields distinctly contracted, the left being more pronounced than the right. There seemed to be some lack of clearness in the media so that the fundi were seen only hazily. The interpretation was of choroidal involvement of possibly specific origin.

Barany Test: The patient showed normally functioning labyrinths.

Radiographic Examination: The skull and sella were normal. The long bones showed a profusion of exostotic processes.

Discussion: The patient presented a clear-cut case of hereditary, deforming chondrodysplasia. There was no evidence anywhere in the examination of any endocrine involvement, the slight thyroid enlargement observed in the physical examination being no more than a slight hyperplasia without toxic features. There was a clear-cut syphilitic condition verified beyond any possible doubt, and this seemed to be congenital in origin, although naturally its presence through acquirement could not be ruled out.

Case B-663—An Achondroplastc Dwarf with Rickets and a Congenital Malformation of the Skull (Hydrocephalus) Producing a Lesion of the Central Nervous System. The patient was a six-year-old boy less than 100 cm. tall, presenting a disproportionately large head. He had been a full-term child, normally delivered, but the large head was noted at birth. He was a very sickly baby for the first two years of his life, and during the first year he had an attack of vomiting after each nursing, which continued for a period of about two weeks. The head was very heavy and up to the age of one year always had to be supported. At the age of 2 light therapy was applied to the spine without any change in the condition. At this time, in the mother's words, the head seemed almost larger than the body. As he approached his third year he began to improve spontaneously. The body has grown but the head remained still disproportionately large. During the last year or two he has been able to play with other children and has even entered kindergarten. He presented some speech difficulties. The ears had discharged and there had been a loss of aural acuity. He has always compained of undue fatigability.

Family History: The parents were living and well and there were two normal siblings. The remaining family history was irrelevant.

Past History: The patient had all of the minor ailments and had always been subject to very severe colds. As noted above, there had been loss of hearing and an intermittent discharge from the ears. The child had always been a mouth breather and there were other evidences of possible partial obstruction. The teeth were very soft and decayed easily. At times the child had had night sweats. The remaining history did not depart materially from the normal.

Physical Examination: The patient presented the appearance of a child with the form of an aged man and with a distinctly large head. There was no suggestion of a progeria as this term is usually understood. There was very poor posture, marked lordosis, knock-knee, and bowed tibiae. The head was symmetrical, prominent in the frontal parietal regions, making the occiput large in comparison with the face. The sutures and fontanelles were closed but marked by depressions. The facial expression was dull. The teeth were in very poor dental repair, the incisors presenting saw-tooth edges. The palate was high and arched, the tonsils large and cryptic. A rosary was noted but there was no Harrison's groove. An occasional squeaky rale was reported. There was distinct tachycardia. The abdomen was bulging with marked ptosis, but was otherwise normal. The epiphyses at the knees were markedly enlarged, the right shoulder drooped, and there was a marked dorso-lumbar lordosis. There was some degree of mental retardation. Articulation was indistinct. Biceps, radial and knee jerks were sluggish.

Laboratory Summary: The boy had a very high sitting height index in part, at least, due to leg deformity. He was 15 per cent below his predicted weight and definitely below his predicted lung volume. It was impossible to get a satisfactory basal rate. The most dependable gave a value of 22 per cent above the more reliable standards. The blood pressure was low, the pulse showed an upward tendency, the temperature was slightly febrile. There was no question that the rate as recorded was significantly above the truth. The urine volume was scanty, elimination fair; a trace of sugar was reported. His protein intake was adequate but not liberal; the residual fraction showed a very high value. The sugar tolerance was greatly depressed; in fact, a few grams of galactose would invariably produce a positive test. The blood chemistry was normal and the blood sugar at the low normal level. The blood showed a slight secondary anaemia, a lymphocytosis presumably influenced by the patient's age, and a 6 per cent eosinophilia.

Ear Examination: The patient showed chronic discharging ears.

Neurological Examination: There was a moderate hydrocephalus. No signs of organic nervous disease were elicited. The patient seemed a little less alert than the average child of his age.

Laryngological Examination: Tonsils were markedly enlarged, cryptic, and infected.

Orthopedic Examination: This confirmed the earlier indications of rachitis.

Audiogram: There was a definite loss of hearing in both ears.

Radiographic Examination: The skull was of the hydrocephalic type with convolutional impressions on the inner table and prominent diploic veins. The sella was normal; the chest was normal; all of the long bones showed deformities of maldevelopment. There were wide epiphyseal spaces between the ilium and ischium.

Eye Examination: The fundi showed tortuous vessels. There was a symmetrical contraction of the form and color fields to less than 10 degrees, precluding the delineation of the blind spots.

Discussion: The child patently had a congenital hydrocephalus, and superimposed upon this was a rachitis. The test gave no evidence whatsoever of any endocrine involvement, all of the departures from the normal being patently referable to demonstrated non-endocrine conditions. It is interesting to note that a complete check-up determination made one year later, confirmed all of the findings here presented, and in addition gave a basal rate at a somewhat lower level than that recorded above. The lack of definition of standards in children of this age forbids too exact interpretation. Our measurements, however, would seem to indicate that the boy's oxygen consumption was probably within the normal range.

CASE B-251—PROGRESSIVE MUSCULAR DYSTROPHY. This condition is one which is frequently assumed to derive from an endocrinopathy. The present report, drawn from one of our cases, is typical of the members of the small group which we have examined, none of whom have given evidence of any present or past endocrine disease.

The patient was a 22-year-old girl, complaining of difficulty in moving both arms, coupled with pain in the left knee. She was also extremely nervous. Some two years previously she had first noticed an undue fatigue at the end of the day's work. The condition had rapidly progressed and in a short time her night's sleep produced no refreshment. Rest was advised for the condition, but was without benefit. Some eighteen months previously the condition was complicated by the development of a pain factor which at first was generalized in character but later localized in the shoulder and then radiated downward through the arms. She also noted a progressive loss of strength in the right hand and arm, which at times seemed heavy and numb. Later, she noted that the muscles of the hand were atrophying, those of the palm being first involved, while later, the thenar and hypothenar eminences began to disappear. The muscle wasting had gradually progressed to involve the fore- and upper-arms. During the month prior to admission pain in the left knee had become a factor.

Family History: Her mother had had a successful removal of a breast cancer 15 years previously. The remaining history was negative. The patient was unmarried.

Past History: She reported the usual minor ailments of childhood, an appendix operation seven years previously, and a nervous breakdown two years before admission. Eight years earlier or six years before the onset of her present condition the patient had scalded her right arm and shoulder. She complained of loss of visual acuity, an occasional severe earache, a susceptibility to head colds, sore-throats and tonsilitis. She experienced dyspnoea on slight exertion. At times was nauseated but not to the point of vomiting. The catamenial history was initially normal with onset at the age of 14, and an uneventful course up to two years previously. At that time there was a brief period of shortening of the intermenstrual interval with spontaneous restoration to normal rhythm within a few months. The patient had lost 34 lbs. in the past two years. During the course of the present complaint she had had occasional attacks of vertigo and had developed a definite emotional instability.

Physical Examination: The patient was a poorly developed and nourished woman of 24. The pupils were dilated and the reactions were sluggish. The teeth gave evidence of much dental attention. The heart and lungs were normal, as was the abdomen. The right arm showed slight wasting of the muscles of the upper arm and marked wasting of the forearm. There was also marked wasting of the interossii, more particularly on the palmar surface. There was an absence of the thenar and hyopthenar eminences, continual flexion of the fourth and fifth fingers and permanent extension of the first finger. Only the second finger showed free motion. The patient was unable to raise her forearm and hand to the face but achieved this by action of shoulder and arm muscles. The left arm showed free motion but moderate wasting in the palm of the hand and of the thenar eminence. The legs were apparently not wasting, but there was tenderness in the popliteal space; also a marked tenderness along the course of all nerves of the hands and arms. There was also tenderness along the ganglia of the 7th and 8th cervical, the first two thoracic and the lumbar nerves. The abdominal reflexes and knee jerks were exaggerated.

Laboratory Summary: The patient was recorded as but 1 per cent underweight, but with her low sitting height index this was less than the truth. There was slight but definite loss of lung volume. The basal rate was normal as were the associated physical findings. The low alveolar carbon dioxide resulted from the inability to collect a representative specimen. The urine volume was scanty, elimination was poor. Both albumin and sugar were noted. The protein intake was inadequate. The nitrogen partition formula was normal. The sugar tolerance was normal. The blood chemistry was normal. She had a secondary anaemia and a 5 per cent eosinophilia.

Radiographic Examination: The skull, sella, cervical and lumbar spine, pelvis, and chest were all normal. She showed one infected tooth.

Barany Test: The labyrinth function was normal.

Eye Examination: The pupillary reactions were very stiff; the discs were chalk white; the fields could not be exactly delineated but were definitely concentrically contracted. In the examiner's opinion there was evidence of a secondary atrophy with the lesion at or behind the chiasm.

Discussion: The examination of this case was incomplete as the result of conditions outside of our control. It is quoted, as stated above, solely to demonstrate the complete absence of any indication of endocrine disease, and as also noted above, the findings here are typical of other cases which we have had opportunity to study.

CASE B-839—REFERRED FOR DIABETES INSIPIDUS. The patient was a 5-year-old boy whose chief complaint was reported as polydipsia, polyuria, and nocturnal enuresis. Up to the age of three the child had been apparently normal. At this time he had an attack of measles, and subsequent to this he had wet the bed once or twice every night. Treatment at the time of onset was not effective and attempts at curtailing his fluid intake in the late afternoon had been abortive, as the child would cry and the mother would give him liquids. During the preceding summer the mother noted that the child was continuously thirsty, that he drank very frequently and passed large quantities of pale urine. Three months before admission he developed acute abdominal pain and passed into a state of coma in which he remained for three days. She informed us the condition was due to "acidosis," but added that the child had previously eaten berries in one of the public parks that had recently been sprayed with arsenate of lead.

Family History: The patient had five siblings, none of whom exhibited his difficulty. The remaining history was negative.

Past History: The child was a full-term, instrumentally delivered baby, breast fed for three months, and then on a variety of artificial prepartions which produced a transitory attack of eczema. The child had measles and whooping cough and the condition noted above at the age of 5. He complained of an occasional headache, was subject to head colds and had recurrent attacks of eczema. During the past year there had been periods when the child would wake at night and complain of pain in the calf of the right leg. Massage would speedily stop this.

Physical Examination: The patient was a poorly developed and nourished child, of apparently normal intelligence. There were numerous eczematous lesions on the face, back and arms. The bridge of the nose was somewhat depressed but there was no apparent obstruction. The tonsils were large and reddened. There was a distinct cervical adenopathy. The boy's posture was bad with a moderate degree of lordosis. The remaining findings were normal.

Laboratory Summary: The boy was 10 per cent underweight, with a slightly depressed lung volume. A fairly dependable basal rate was within normal limits. The urine volume, while ample for a child of this age, did not confirm the report of a marked polyuria. Albumin was present. The nitrogen partition was normal. The sugar tolerance was slightly low. Blood chemistry was normal, the slightly high blood sugar undoubtedly deriving from the patient's emotional response to venipuncture. The blood morphology showed an increase in both the eosinophiles and the endothelial leucocytes.

Skin Examination: The condition was defined as eczema of the erythematosquamous type.

Neurological Examination: Normal.

Orthopedic Examination: Normal.

Chest Examination: Normal.

Abdominal Examination: Normal.

Nose and Throat Examination: Normal.

Eye Examination: Incomplete but so far as obtainable, normal.

Discussion: It was impossible to secure x-ray pictures of this child as he was very restless during the first attempts and the mother would not give her consent to a repetition. The only real departure from the normal which the child presented was the slightly depressed sugar tolerance. This could well arise from a variety of causes, and there was nothing in the remaining examination to imply an endocrine significance to it. We do not regard this case as one of proven diabetes insipidus, although the verbal report of the referring physician indicated that there had been times in the child's life when the urine output was much more suggestive than at the time of our study. There was certainly no evidence here of any pituitary involvement. The case is offered as one in which endocrine medication might well have been exhibited on the basis of the putative history and yet which on examination failed to offer any evidence to warrant such a procedure.

It will be noted that in the preceding protocols little or no reference is made to treatment. The immediate concern of these studies has been the diagnosis of endocrine disorders, and the response of the patient to endocrine therapy has constituted a therapeutic test offering some measure of support to the accuracy of the diagnostic conclusion. In the present series of cases the diagnostic interest rests upon the fact that the patients simulate or suggest endocrine disease, but demonstrate on analysis a non-endocrine etiology for their presenting condition. The treatment of this numerous group of non-endocrine disorders would follow the conventional lines of current practice and consequently is not germane to our thesis.

Before bringing this article to a conclusion the authors wish to stress the implications of the present paper. That a patient presents outward evidences of, or symptoms suggesting, an existing endocrinopathy, does not in any way prove the existence of such a state, nor does it serve as a warrant for the exhibition of endocrine preparations therapeutically. This latter practice followed empirically and without the warrant of an established diagnosis, at the best can only prove abortive in correcting the patient's difficulty, and at the worst may do grave and serious damage to a diseased organism. It should be hardly necessary to repeat this caution, and yet a large number of patients referred to us who report in their histories the administration of powerful glandular products without other warrant than an uncritical expectancy, indicate the urgency. Endocrinology is a field in medicine in which great benefit may be wrought by the correct use of its powerful therapeutic agents and even greater damage done by their misuse.

Reprinted from ENDOCRINOLOGY, The Bulletin of the Association for the Study of Internal Secretions, 1214 Wilshire Medical Bldg., Los Angeles, California, Vol. 13, No. 3, May-June, 1929, Pages 263 to 284.

STUDIES OF THE ENDOCRINE GLANDS

VIII. The Differential Diagnosis of Endocrine Disorders

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SECTION I

In an earlier communication (1), the author described in some detail an objective method for the differential diagnosis of disorders of the several endocrine glands and the separation of such endocrinopathies from the numerous non-endocrine conditions simulating them in their clinical and laboratory evidences. Later papers, in collaboration with Dr. C. H. Lawrence, have presented the results from the application of the method severally to functional disturbances of the pituitary (2), the thyroid (3), the gonads, male and female (4), the adrenals (5), and a group of so-called ''pluriglandular'' syndromes (6). A subsequent article (7a, b) has dealt with an analysis of a series of cases each of which offered clinical or laboratory evidence suggesting an endocrinopathy but which on thorough study gave positive evidence of an underlying etiology unassociated with the ductless glands.

The present communication is designed to amplify and summarize the earlier papers and present in as concrete and practical form as may be possible the results of experience gained in studies that have been actively carried on since 1912.

As the present series of cases from which these conclusions are drawn includes well over 4000 patients who have been thoroughly studied, the collation of material and its presentation in reasonably simple and compact form offers certain difficulties. While some of the data can be tabulated satisfactorily, much of the material cannot be. Variations in the functional level of a single gland often fail to produce correspondingly varying changes in many of the objective data. A further complication lies in the variable relationships of such composite glands as the pituitary and the adrenals. All of these factors lead to end results that in the summation of a general series may be mutually compensatory and so yield figures the apparent normal level of which is wholly misleading. The marked deviation from normal performance shown in the individual case is thus obscured and its true significance lost.

To summarize the complete picture of each gland as a separate entity would defeat the present purpose. Each point would require discussion on the basis of comparison and contrast with all of the glands as the method is essentially one of differentiation. This could only mean a wearying duplication.

On the whole, it has seemed best in presenting the material to follow the actual method of practice, making running comment on such points as have an actual significance or a possible suggestion. In the interest of simplicity, also but scanty reference will be made to the existing diffuse endocrine literature. Citations will be made from the papers in the series of which this is the summary, but solely because they are expository to the text. The basis for inclusion of the few remaining references will be apparent from the context.

As will be recalled from the earlier description (1), the examination of each patient calls for a comprehensive and detailed history and a thorough and painstaking physical examination. These partly subjective evidences are supplemented by the objective facts drawn from a somewhat extensive series of standardized laboratory tests and measurements which experience has shown to be significant. The material from both of these sources is essential to a just estimate of the underlying condition. To the basic routine study to which each patient is submitted, a number of special tests and clinical studies are added, these being determined by the needs of the individual patient. They consist of selections from the many well-known laboratory procedures such as special kidney and liver function tests, cardiogram and gastric analysis, and also from the many special examinations carried out by the members of the consulting staff. Each step in the study is taken expectantly as it may either confirm a tentative diagnosis, eliminate a possibility suggested by the results of the earlier study, or, at the worst, indicate other lines of investigation leading to an ultimate resolution of the problem. In the course of the work, certain of these consultations and special tests have demonstrated so general a significance as to lead to their incorporation as a part of the routine. In this latter group, for example, falls the eye examination, including the measurement of visual acuity, examination of the pupils, ophthalmoscopic study, delineation of the blind spots and plotting of form and color fields, the several results of which may throw light on a wide variety of conditions. As will be shown later in the paper, the routine eye examination has established a number of new facts of very real diagnostic significance.

The last phase of the study is concerned with the critical analysis of the collected material and leads to a diagnosis, the authority of which rests on that of the supporting evidences from which it is derived. It is again emphasized that each single test or measurement must be interpreted in the light of all related observations. For example, a low basal metabolic rate in an obese person is interpreted with regrettable frequency as an evidence of thyroid failure. As a matter of fact, it could result from partial protein inanition, with or without a complicating endocrine condition not associated with the thyroid. Obesity is wholly compatible with an inadequate protein intake as the daily fat and carbohydrate content may far exceed the energy requirement of the individual. Inadequate protein will lower the basal rate independently of the remainder of the diet (8).

Further, non-endocrine causes of departures from the normal must be rigorously eliminated by test and observation—not opinion—before the point in question can be given any weight in support of an endocrine diagnosis. The paper already cited (7a, b) offers ample evidence to support this contention.

Finally, it must always be borne in mind that the subjective evidences of the patient's own story are the least dependable of all of the material available. Honest lapses of memory coupled with the suppression of facts and with frank misstatements intended to mislead are all vitiating factors. In a consecutive series of 40 cases of syphilis—from which children with congential lues were excluded—31 subjects denied a previous infection.

While the subjective data are the least controlled, serious error may also appear indirectly in the laboratory measurements. Failure to collect a full 24-hour urine sample, sophistication of collected material and failure to take all of a provocative test meal, when carried out at home, are all potential sources of misleading figures. Constant vigilance is essential if reliable data are to be secured.

Finally, while the subjective clinical evidences are less reliable than the objective laboratory data, both may be essential to the resolution of the diagnostic problem. One other matter presents itself for careful consideration. The presence of organic or functional disease of an endocrine gland in an individual patient does not preclude the presence of other disease conditions unassociated directly with it. In fact, very many endocrine cases will demonstrate the presence of an intercurrent disease which may equal or even exceed in importance the glandular derangement. As these superimposed conditions all may influence in some measure the various individual data that make up the disease picture, due account must be taken of them.

To render the matter concrete, a group of 500 endocrine cases has been taken from a consecutive series and the relative frequency of the complications which they presented ascertained. These figures have been compared with the 500 non-endocrine cases which were discussed in an earlier paper (7a, b). The result of the study is given in the table.

No definite conclusions can be drawn from the small number of cases in the adrenal and pancreas groups, but the frequent occurrence of tuberculosis and of kidney disease in the adrenal group and of syphilis and cataract in the pancreas group seems significant. In the main, there is a large degree of correlation between the complications and the endocrine disorders. When any given complication occurs much oftener in the endocrine than in the non-endocrine group, it seems logical to assume a causal relationship. In interpreting this table, however, special circumstances in some cases have to be considered. The larger number of mentally retarded patients in the endocrine group rests on the fact that such cases were referred for study only where various stigmata suggested a possible glandular background. Likewise, primary anaemia and ear disease occur with abnormal frequency in the non-endocrine group. We have made a special study of these conditions. The number of non-endocrine syphilitics may probably be traced to the fact that the disease frequently simulated disorders of the ductless glands. The non-endocrine arthritics were reported only when the condition was severe, hence the apparent incidence is misleading. The "uncomplicated" cases in the non-endocrine group were normal controls and thus do not correspond to the endocrine group similarly designated. The patients showing malnutrition were

TABLE I

Percentage Complication of Primary Endocrine Cases

Compilcation		Endocrine Group						Non-Endocrine Group (%)
Group	Condition	Pit.	Thy.	Gon.	Adr.	Pan.	Total	
Number of Cases		185	160	125	15	15	500	500
Infections	Tuberculosis	5	8	6	40	0	7.0	5.2
	Atrophic Rhinitis	0	1	3	0	0	1.0	0.8
	Arthritis	9	7	11	13	13	9.0	4.8
	Tonsils	11	11	9	0	13	10.4	5.0
	Sinuses	9	10	5	7	7	8.0	
	Other Focal Infections	9	3	6	0	20	6.6	
Psycho-Neuroses	Neuroses	8	6	23	0	7	10.8	4.4
	Psycho-Neuroses	9	6	13	13	0	9.0	6.6
	Psychoses	5	3	2	0	7	3.8	3.2
Nervous System	Lesions of Brain and Cord	17	11	2	20	0	10.8	10.0
	Epilepsy	3	1	2	0	7	2.2	2.0
	Mental Retard	6	4	0	0	0	3.4	1.6
	Physical Retard	3	3	0	0	0	2.0	0.0
	Physical Overgrowth	1	1	0	7	0	0.8	0.4
	Chorea	3	1	0	0	0	1.4	2.6
Metabolism	Malnutrition	1	0	6	7	7	2.4	6.0
	Obesity	25	11	4	0	20	14.6	12.2
	Misc. Bone Diseases	2	3	1	7	0	2.2	2.0
Cardio-Vascular System	Heart	8	4	4	0	0	5.2	1.8
	Kidney	8	8	13	53	13	10.6	10.6
	Cardiorenal	1	4	4	7	7	3.0	8.2
	Hypertension	8	7	4	0	7	6.2	6.0
Blood	Primary Anaemia	0	1	0	0	0	0.2	1.6
	Hemophilia	0	0	0	0	7	0.2	0.2
Tumors	Malignant	1	3	1	7	0	1.6	1.2
	Benign	3	1	0	0	7	1.6	2.0
	Non-Toxic Goiter	4	0	5	0	0	2.6	1.6
Miscellaneous Conditions	Eye	1	3	4	7	20	3.0	2.8
	Ear	3	8	4	0	0	4.6	13.0
	Skin	5	8	5	0	7	5.6	4.6
	Allergy	3	6	5	0	0	4.2	2.4
	Gastro-Intestinal	1	7	6	13	0	4.6	3.0
	Liver and Gall Bladder	10	29	10	0	27	16.4	2.6
	Syphilis	5	4	3	0	40	5.2	11.4
	Pelvic Disease*	9	2	12	0	0	7.2	3.2
	Menstrual*	4	2	4	0	11	3.6	6.0
	Infertility†	4	6	8	0	0	5.5	1.2
	Pregnancy*	1	1	0	0	0	0.8	1.0
	Uncomplicated	5	13	9	0	7	8.4	3.6

*Based upon females alone.

†Based upon number of patients married.

those in whom the diagnosis was based on several manifestations. If reduced weight alone were considered the difference in the endocrine and the non-endocrine groups would be much less.

Turning to those groups where the lack of correlation is seemingly a real one, a few comments may be permitted. The low proportion of focal infections in the non-endocrine group is somewhat misleading since special studies by which they might have been discovered were fewer in number than in the endocrine group. Even making allowance for this fact, however, focal infections occur in the endocrine group definitely more often than in the non-endocrine.

The excess of cases of heart disease in the endocrine group does not depend upon the thyroid factor as might at first be anticipated. It will be noted that the combined cardiac and cardiorenal sub-groups are about equal in the endocrine and the non-endocrine groups. There is no doubt an age element in the distribution, as the non-endocrine subjects were older, and it is possible that the difference here is apparent rather than real.

As will be discussed later, the endocrine group and especially the ovarian patients had had a large amount of abdominal surgery and this may enter as a determining factor in the disproportion of pelvic disease. The unequal number of cases of infertility is not as representative as these figures would seem to indicate, but there is a real difference even without the element of special selection that was operative in this series. The patients with neuroses and liver disorders show real differences, and these will be treated in the body of the paper.

Reverting to the table, the correlations of each complication with the several individual endocrinopathies may be briefly reviewed. Certain of them, such as the high incidence of tuberculosis and renal disease in adrenal failure, could well be predicted. The selective influence of ovarian failure in producing functional derangements of the nervous system is apparent. The association of psychosis with all of the endocrines, but somewhat more with pituitary disease, has been noted in the earlier papers. The raw data are in interesting agreement with the preliminary figures of the far more comprehensive studies of Hoskins and Sleeper (9) recently presented.

The anatomical relationships of the pituitary undoubtedly account for the large number of these patients showing lesions of the central nervous system as complicating factors. The fact that mental retardation appears only in the pituitary and thyroid groups is presumably due to the fact that ovarian failure does not occur at any early age. While the evidence is not yet entirely conclusive, the studies of this institution seem to indicate that the ovary in the human race assumes a real hormonic importance only at puberty. The testicle, on the other hand, has little or no endocrine significance in adult years. The few dependable data obtained from studies of prepubertal castration in man, however, seem to indicate a genuine endocrine function before maturity.

Physical retardation falls in the same category and the sole adrenal case presenting overgrowth was the child (Case C-16) already discussed in an earlier paper (5). The malnutrition of the ovarian case is probably due to neurotic dietary eccentricities. While neuroses are not confined to ovarian failures, they are most often found in this group. Victims of ovarian failure are notably egocentric. The relative influence of the several endocrine glands in producing obesity is well illustrated. The low incidence of hypertension in the gonad group correlates both with the characteristically low blood pressure of that condition and the freedom from the arteriosclerotic changes that often occur in hypothyroidism.

In the cases of non-toxic goiter here recorded the thyroids showed considerable degrees of enlargement. The question of slight thyroid hyperplasia will be considered later. Thyroid patients are seemingly more susceptible to deafness, various forms of skin disease and protein sensitivity. No reason for the low incidence of gastrointestinal disorders in pituitary disease can be offered at present.

The frequent association of gall bladder disease and hepatic dysfunction with thyroid failure has already been noted (3) and finds added support in the present compilation. The relative incidence of severe menstrual disorders in the several groups serves once more to emphasize that these conditions are not essentially due to ovarian failure.

One point requires emphasis. In discussing these data, no attempt has been made to determine specific causal relationships. The data, however, do seem to warrant two conclusions:

1. The occurrence of most non-endocrine complications in the endocrine group and in the non-endocrine group in so nearly equal numbers indicates that significant increase in the presence of a symptom or a positive response to a test in the endocrine group is probably due to the glandular factor.

2. Certain non-endocrine disease states seem to be associated selectively with individual endocrinopathies, although usually represented in them all.

With this general introduction, attention may be directed to the consideration of the pertinent clinical evidences.

Sex. That endocrine disorders are reported more often among females than males there can be no doubt. The figures of this institution show a ratio of three females to one male, and that this is not due solely to psychological factors is attested by the fact that in our parallel non-endocrine group the ratio is three to two. Only the diabetics show an exception, the female incidence here being slightly less than in the non-endocrine group. Significant departure from the group average is shown by the pituitary which approaches the non-endocrine frequency (63 per cent) and by the gonad group which is composed almost exclusively of women (96 per cent). The apparently extreme rarity of functional or organic change in the testicle of sufficient magnitude to require medical aid has been discussed elsewhere (4).

Age. About 60 per cent of the pituitary cases come to investigation before they are thirty; the thyroid scatter is fairly uniform throughout the first six decades; the ovarian diseases seemingly do not begin until after the establishment of the catamenia, but nearly 40 per cent are reported during the third decade; adrenal disease is chiefly an incident of the years from 20 to 50. In general, as shown in our series by comparison of 1250 endocrine with 1000 non-endocrine cases, endocrinopathies have a somewhat earlier onset than other diseases.

Age of Onset and Duration. The reports on this event are unduly colored by the subjective character of the basic datum, most strikingly illustrated in the patients who report the chief complaint as dating from birth. A further cause of error lies in the very human tendency to ascribe the cause to some striking event in the life history which in many cases is wholly unassociated with the true condition. Including the congenitally defective and those claiming onset at birth, in 38 per cent of the pituitary cases the beginning of the chief complaint is dated before the eleventh birthday, while but 20 per cent of the thyroid and 10 per cent of the gonad disorders fall in this decade; the non-endocrine record shows 14 per cent. Sixty-four per cent of the gonad disorders are reported as beginning in the second and third decades; all of the remaining percentile values show an approximate uniformity, the major differences being compensated before the thirty-first birthday. The concentration of the gonad cases in the latter half of the second and the whole of the third decade, normally the period of largest fertility, is possibly suggestive.

As the duration of the disorder is calculated from the alleged date of onset, it is equally subjective. For what value may be in them, it may be recorded that assuming conventionally for intervals (a) less than one year, (b) from one to five, (c) five to ten, and (d) over ten years, the endocrine distribution is practically uniform throughout. The non-endocrine group concentrates in the second period (43 per cent) at the expense of the first (13 per cent).

Chief Complaint. The patient's presentation of the case hinges directly on the chief complaint or, in the great majority of instances, complaints. From its subjective character, this may be the least important piece of evidence in the entire study, depending as it does on a variety of mental factors as well as physical elements. The neurasthenic with a long circumstantial tale in which real and fancied disabilities are hopelessly interwoven stands at one extreme while the emulator of the Spartan youth imbued with a morbid fear of self-revealment defines the other. Ladies over 100 per cent above their predicted weight scorn to list obesity among their disabilities, while others, fully 20 per cent below their predicted normal, offer overweight as the reason for their reference to the clinic.

With the dominance of the subjective element, a wide scatter is to be anticipated in the symptoms as offered. Certain of them, however, recur with a frequency that both breeds confidence in their existence and also lends to them a possible diagnostic significance.

With a just recognition of all of these factors, and in the interest of economy of space, discussion will be limited to those individual points which show differences of diagnostic significance. More complete and detailed analysis must be reserved for later presentation. The omission of a large number of symptomatic data does not mean that they have been ignored in the analysis but that their inclusion would be confusing. This applies particularly to the many non-endocrine conditions discussion of which must be limited to basically significant differences.

Fatigue. Reports of asthenia and of fatigability wholly disproportionate to previous physical exertion is a common complaint in all of the endocrine disorders. Least in evidence in pituitary disease (48 per cent) and most in adrenal disorders (93 per cent), it definitely suggests an endocrinopathy. Non-endocrine states with very high incidence of fatigue are tuberculosis, cancer, and primary anaemia.

While no attempt should be made to delimit the picture too sharply, the fatigue story of the several endocrine entities shows certain possibly suggestive differences. In pituitary disorders, a loss of endurance is a marked feature. There is no asthenic crisis as with the adrenal, but the day's productivity becomes less and the effort greater to produce even a meager return. The thyroid patient awakes unrefreshed, but as the day progresses there is an improvement. At some time, varying greatly among individuals, an apex of well-being is reached which, while never high, contrasts favorably with the condition on awakening. The peak, however, is soon passed and the patient rapidly declines to a level of real exhaustion which persists. In ovarian disease the patient is just "tired all the time," a subjective element being especially noticeable. Finally, the adrenal case in the earlier stages shows an intermittency; brief periods of well-being are rapidly followed by periods of real exhaustion from which the patient recuperates only to repeat the cycle. As the condition progresses, the asthenic intervals become longer and finally determine the terminal condition.

Tremors. While the condition is pathognomic in hyperthyroidism, and of frequent report in the dysfunctional states of this gland, all of the endocrine group, particularly the ovarian failures, show a fairly high incidence. Asthenia and nervous instability, from whatever cause, are factors in its production.

Nervousness. This is one of the most subjective of all reported symptoms. It is an omnibus term, including a number of aspects of nervous instability and not infrequently is offered as an excuse for selfishness, undue irritability, and kindred personality defects. A by-product of numerous non-endocrine disorders, it is dominantly present in all of the endocrine, least apparently in the pituitary cases, and an invariable feature of ovarian failure. The psychoneurotic group and that of the central nerve lesions account for the main portion of the non-endocrine cases, but syphilis and cardiovascular disease each make an appreciable contribution to the total.

Paraesthesias. Numbness, formication, and cramps are frequently reported by thyroid and adrenal patients, less often in the other endocrine states. As symptoms, they occur with like or even greater frequency in a number of non-endocrine conditions.

Pain. In the endocrine group pain is frequently not localized with any marked specificity but is rather a generalized condition. Of frequent report in hyperpituitarism and Addison's disease, the highest incidence is found in the group of ovarian failure. In fact, any symptom associated with a pain impulse is usually found most frequently in this group. Thus, headache is common among the hypogonad patients, exceeding in frequency the report of the pituitary group, in which there may be a material cause for the symptom.

Obesity. All of the major endocrine groups show a high incidence of this symptom, although its report as a complaint lags far behind its actual frequency of occurrence. The pituitary leads with nearly 50 per cent, while one in three of the thyroid subjects and one in four of the ovarian failures are at least 15 per cent overweight. The selective girdle distribution of the pituitary may merge to a suggestion of the generalized thyroid type in patients who are more than 100 per cent above prediction.

In ovarian failure a fat body with thin legs is common. Localized evidences such as the supraclavicular pads of thyroid failure are easily obscured in the truly obese. Critical analysis demonstrates the unwisdom of basing a diagnosis on fat distribution. A large number of non-endocrine states are associated with overweight, not the least significant of which is simple gluttony.

Underweight. While rarely figuring as a chief complaint, it is of relatively frequent occurrence. Many hyperthyroid cases show underweight and as many thyroid failures were below as were above prediction. Early in these studies a type of thyroid failure was recognized on objective grounds which departed notably from the conventional picture of hypothyroidism. These patients were thin; mentally and, in some measure, physically, alert, not sluggish; did not exhibit myxedema and offered yet other significant departures from convention. They presented, however, typical laboratory pictures (including basal rates below —30 per cent) and showed a normalizing of the clinical and laboratory picture, including gain in weight, under the stimulus of thyroid therapy. The condition has been described elsewhere (3, 10). Rapid upward changes in weight are suggestive of a modified endocrine status, while the opposite condition suggests equally wasting non-endocrine disease or an endocrinopathy.

Overgrowth. This does not include early sexual maturity and usually implies a pituitary disorder. An influence of the testicle in prepubertal years has been recorded by others. Unfortunately there are no cases in this series in which a testicular involvement could with certainty be dated prior to maturity. In this particular field, in which unbridled speculation has played so dominant a rôle, it seems best in this summary to adhere to observed facts.

Undergrowth. Both thyroid and pituitary diseases are associated with this state as, equally, are injuries to the central nervous system and syphilis. As might be anticipated, the ovary seems to play no part in producing this condition.

Mental Retardation. Again, only the pituitary and thyroid seem to be involved. An interesting fact is that but half of the children referred as feeble-minded are found to be so on careful psychometric study.

Disorders of the Eye. The results of actual measurements will be considered later. Pain, blurring of vision, and spots before the eyes are frequently reported in the ovarian cases. The association of cataracts with diabetes is well known. Poor vision is a uniform report, the pituitary showing no superior influence traceable to its anatomical relationships. Fatigue is also a common and characteristic symptom.

Disorders of the Ear. Tinnitus is a common endocrine complaint most often reported in the ovarian cases, as also is a record of pain.

Disorders of the Nose. The entire endocrine group is seemingly susceptible to colds and to catarrh. Over 50 per cent report one or the other or both. Both the pituitary and gonad groups report epistaxis with significant frequency.

Teeth. While one in ten of endocrine and non-endocrine subjects alike have had all the teeth removed, a poor condition of these important structures is much commoner in the endocrine group. The ovarian cases lead, the thyroid group comes next, while those with pituitary disease are but slightly superior in relative numbers to the non-endocrine group.

Goiter. Inasmuch as a thyroid enlargement is frequently the sole basis of a diagnosis, it is interesting to note that while 11 per cent of the thyroid subjects complained of this condition, 3 per cent each of the pituitary and ovarian patients made a similar report (See "physical examination" later).

Disorders of the Cardiorespiratory System. Dyspnoea without palpitation is a strikingly frequent secondary report in ovarian failure, as is pain in the chest. One in eight of the thyroid patients reported either dyspnoea, palpitation, pain, or cough as a chief complaint, while the pituitary and gonad figures are respectively 0 and 5 per cent. Cough is significant as a report only in hyperthyroidism.

Disorders of the Gastrointestinal System. As a chief complaint, conditions associated with the alimentary tract are encountered in all of the endocrinopathies, the pancreas and adrenal leading. Nausea and vomiting are frequently recorded in all; the ovarian group leads in the report of pain, the adrenal in flatulency.

The reports of jaundice are really interesting. As an earlier incident, it was reported by a smaller group of pituitary subjects than were actually demonstrated to have disorders of the liver and gall bladder. This was repeated much more strikingly in the thyroid group where the relative percentages were 10 and 29 respectively. It is certain that a portion of the hypogonad subjects interpreted sallowness of the complexion (and possibly earlier chlorosis) as jaundice, although the group as a whole showed a 10 per cent incidence of demonstrated hepatic dysfunction (See Table I). Two of the pigmented adrenal patients reported their skin condition as jaundice and, on the other hand, the two diabetics reporting this condition were but half of the number presenting the "bronzed" type of the disease.

Constipation is a usual, diarrhoea a rare report. In the former condition the thyroid and gonad groups show the highest incidence. It is to be remembered that the term is a relative one. Adrenal patients have genuinely poor appetites.

Disorders of the Genito-Urinary System. The concomitant involvement of the kidneys in adrenal disease is the outstanding feature. Nocturia is common to all, dysuria characterizes the ovarian patients.

Disorders of Menstruation. This topic will be discussed more fully later. They were a chief complaint in 15 per cent of the ovarian cases and 10 per cent of the pituitary. Nearly half of the former complained only of dysmenorrhea, this fact influencing in a misleading manner the figures for the chief complaint.

Abnormal Temperature Sensations. The adrenal, gonad, and thyroid patients complained of cold in the order named. If "hot flashes" be eliminated, the opposite condition was rarely mentioned.

To summarize the foregoing briefly, the following may be stated:

In the main, the patient's complaints fail to indicate any real endocrine influence. Definite exceptions are found in reports of fatigability, disorders of dentition, dyspnoea alone and pain in ovarian failure, susceptibility to infections of the upper respiratory tract, mental retardation in pituitary and thyroid disease, overgrowth in pituitary disease, and the general observation of obesity with possibly a significantly selective distribution. Less certainly or significantly should be named "nervousness," nocturia, hypothermia, together with canker, skin diseases, and cough associated with the several types of thyroid disease. Further, no one of these conditions can be regarded as more than suggestive, very appreciable representation of each of them being found in the non-glandular group. In other words, the positive yield is small and concerns itself with trends, not definitions. On the negative side, however, the case is much more hopeful as every symptom points the way for further investigation, the concrete return of which may be the definite inclusion or exclusion of really significant factors. The suggestive quality of this type of evidence cannot be overestimated; it is vital to an adequate consideration of every case. But its straightly defined limitations should ever be borne in mind and give pause to an enthusiasm that would erect a final diagnosis on so uncertain a foundation.

Family History. Cancer and tuberculosis are very generally reported in both major groups. Diabetes is found in 9 per cent of the endocrine and 7 per cent of the non-endocrine group, while the similar figures for familial thyroid disease are 7 per cent and 3 per cent. Recognizing that pituitary disorders have been less frequently recognized in the past from their usual lack of easily recognized stigmata (acromegaly being of course an exception), the figures for a familial endocrine influence certainly fall short of the truth. Even so, the data obtainable are striking and evidence a real influence in the establishment of what may be termed a constitutional endocrinopathic tendency which is not specific to the gland involved.

A family history of endocrine disease is obtained in pituitary disorders, 21 per cent; thyroid, 14 per cent; ovary, 17 per cent; adrenal, 13 per cent; pancreas, 33 per cent; non-endocrine group, 10 per cent.

Obesity is reported as a family trait seven times as frequently in the endocrine as in the non-endocrine group. It, like non-toxic goiter, however, is greatly influenced by outside considerations; the large disproportion is none the less suggestive.

Past History. In largest measure, these data realize their true significance only in providing a background in the individual case. For example, castration determines an unmistakable endocrinopathy in the individual subjected to it, but the fact is without meaning in indicating any trend of import for differential diagnosis. Earlier encephalitis influences the individual greatly but does not bear on the general problem. Rarely does analysis yield figures which warrant interpretation in terms of general or specific endocrine cause or effect. The following discussion will be limited to the few observations which are seemingly pertinent.

(a) *Previous Diseases.* A history of earlier tuberculosis is found with unique frequency in the group of adrenal cases.

Tonsil and sinus infections appear with much greater frequency in the endocrine group; the distribution is general.

The report of earlier venereal disease is significant only as it emphasizes the unreliability of personal report on this point.

The remaining conditions, nineteen in number, show a general scatter that is devoid of significant trend.

(b) *Surgical History.* Nearly half of the endocrine subjects had had one or more tonsillectomies, a much higher proportion than in non-endocrine cases. The same disparity was evident in sinus operations, though the total number was much smaller.

The ovarian subjects showed a much larger percentage of appendectomies than any other group; in fact, they nearly equaled the sum of the thyroid and pituitary patients reporting it. Further, they reported nearly three times as many repair and suspension operations and hysterectomy had been performed in 8 per cent as against 2 per cent in the thyroid and 1 per cent in the pituitary groups. Seven per cent had had one ovary removed, the total relative incidence in the other two major endocrine groups together. Finally, 15 per cent had been castrated, this last, of course, being a record confined to this group alone.

The association of ovarian failure with abdominal section is worthy of brief further consideration. Omitting complete castration and dilatation and curettage (in which hypo-ovarians show a marked superiority in numbers), the following relationship obtains:

Table II

Percentage of women showing at least one operation requiring abdominal section.

Pituitary	17%
Thyroid	14%
Ovary	42%

The patent association here is frankly susceptible of two interpretations. The first, namely, that ovarian failure predisposed to the development of disease in the abdominal and pelvic organs would have a far firmer foundation if the operations recorded were confined to the internal genital apparatus. This is, however, far from being the case. On the other hand, it seems a supportable thesis that the manipulation incident to the various operative procedures, possibly through indirection, may lower the functional levels of these important glands. The question cannot be settled here, but waiving factors of causation, it seems fair to say that a history of abdominal interference offers a suggestion of possible ovarian failure.

(c) *Traumatic History.* The pituitary cases definitely exceed the other major endocrine groups in the report of head injuries and equal the non-endocrine group which contains a number of patients with traumatic injuries of the central nervous system.

History of the Catamenia. This will be only briefly touched on as the topic is to be treated in detail elsewhere. An analysis of some nine hundred endocrine cases shows nearly 10 per cent maturing before the 12th birthday. Only the ovarian group shows significantly lower figures (5.5 per cent). Nearly 20 per cent show a delayed onset, with the function not established before the 15th birthday. Recognizing that these limits are conventional, they none the less serve to establish relative values. Incidentally, the figures in the non-endocrine group are substantially the same, a fact which urges conservatism in the interpretation of an abnormal menstrual history.

Further considerations deal with the interval of the rhythm and with the duration and amount of the flow. Waiving the niceties of a detailed statistical analysis, the following conclusions may be noted, recognizing that they define tendencies only:

Endocrine disease in general is associated with a larger percentage of menstrual irregularity than is found in an equivalent non-endocrine group.

Pituitary disorders tend to produce a prolonged interval with normal or progressively scanty flow.

Thyroid disease is associated with a true irregularity, the interval being both longer and shorter in the same individual and the flow at times scanty, at others profuse. This latter is far more characteristic of thyroid disease than of any of the other endocrine states.

Failure of the ovaries follows the general course of the pituitary cases, but the scanty periods manifest themselves earlier after the interval has begun to lengthen.

The adrenal cases differ only in degree from the pituitary, with increasing interval and usually normal flow.

Many non-endocrine conditions produce similar pictures but with definitely lessened frequency of appearance.

The one basic fact to be learned from this consideration is that menstrual irregularity does not inevitably imply a primary ovarian failure. Actually about 40 per cent of the hypogonads are entirely normal and another 40 per cent abnormal only in either interval or amount.

Marital History. This topic also will be touched upon very briefly as extensive studies are shortly to be reported. About 50 per cent of all of the groups under consideration had been married one or more times. A single exception was the adrenal group with but 29 per cent. Fertility data are not highly significant as the study of the single patient deals with but one partner. As presumably, however, the same factors operate in each group, the relative data have a modest significance.

The endocrine patients were definitely less fertile than those with non-endocrine disease even though the latter group contained an appreciable number of syphilitics and patients with other conditions recognized as influencing fertility. The pituitary shows the same relative number of conceptions per marriage as does the non-endocrine group; the other endocrinopathies a lower value, the thyroid, gonad, and adrenal following in the order named. All of the adrenal pregnancies were successful (the small number involved robs this fact of real statistical significance) and three in four of both the pituitary and thyroid pregnancies terminated in viable children. Only two in three impregnations of the ovarian subjects yielded living issue, there being a high incidence of miscarriage. As their percentage of reported abortions was also the highest, it may well be that the large total of miscarriages was more apparent than real. Whatever the agency, nearly half of the ovarian cases were unproductive, about one-third of both the pituitary and thyroid groups, and only one-fourth of the non-endocrine series.

It seems warrantable to conclude that endocrine disease constitutes one hindrance to a fertile union and that ovarian disease seems to exercise a larger measure of influence than do the other members of the group. The second is tentative and possibly subject to revision; the first is established.

PHYSICAL EXAMINATION

While the data under this caption are far more objective in character, there yet remains a subjective element for which due allowance must be made in interpretation.

Development and Nutrition. The actual development of the individual as reported here is in largest measure a matter resting on the judgment of the examiner and inevitably influenced by the state of the patient's nutrition. Gross developmental defects are patent, but in the inspection of the average non-deformed individual the criteria for designation will show a fairly wide range. If the usual assumption be made that these adverse factors will operate uniformly in groups of sufficient size to absorb individual variation, the figures assume a certain significance. The endocrine group records a slightly larger incidence of individuals showing good development than does the non-endocrine, the pituitary leading by an appreciable margin. This record is remarkable as the endocrine glands are conceded to be potent regulators of growth and development. It must be remembered, however, that the large majority of the endocrine cases studied were in adult years and the onset of the prevailing difficulty had very frequently postdated the growth period. With this consideration the apparent contradiction disappears and the conclusion to be drawn from the developmental report is that it has no selective significance in any general sense. Naturally, reservation is made in favor of the dwarf or the giant, but this condition affects the individual, not the group. The achondroplasics of these series were all without evidence of any endocrine disorder and showed a relatively high incidence of luetic taint.

The nutritional values reflect the early reports on weight. The pituitary shows the most pronounced tendency toward overweight, the adrenal the least. The thyroid partition is striking in that the three percentile values for normal, overweight, and underweight are 34, 33, 33, a fact that is somewhat far reaching in its significance.

The thyroid cases show a higher association with eczema, psoriasis, and keloid, the gonad patients with acne. There is no real differential significance as all of the groups show an incidence of some kind of skin eruption equal to one in four.

While only the adrenal patients showed frequent pigmentation, a few hyperthyroid subjects exhibited skin changes characteristic of this condition. Four of the diabetics were of the bronzed type; they were all referred as potential cases of Addison's disease.

Marked varicosities, chiefly in the lower extremities, are frequently observed in pituitary disease. Slight varicose enlargement is a fairly general finding throughout the entire endocrine group.

The amount and distribution of the hair in various parts of the body requires the exercise of great caution in its interpretation. Such factors as race, employment, and similar wholly extraneous agencies may profoundly affect either standards or occurrence.

Broadly speaking, thyroid failure tends to produce loss of hair from the vertex in individuals whose age does not make the occurrence a natural one. The interpretation of abnormal arrangement of the eyebrows in terms of thyroid failure has notably less to recommend it as a sound diagnostic procedure.

Hair on the face usually follows the course of that on the body, although females with facial hypertrichosis and normal body hair are not uncommon. General hypertrichosis and particularly a male distribution of pubic hair is most certainly associated with pituitary disease and with ovarian failure. Its attribution primarily to tumors of the adrenal cortex is not warrantable (4), although they are seemingly also a factor. Scanty body and facial hair is associated both with pituitary and thyroid conditions, more marked in the former and chiefly in cases of an underactivity beginning in the earlier years of growth and development. Loss of body hair in the adult, in the writer's experience, is more frequently met in pituitary than in thyroid disorders, although observed in both. In relation to the pubic hair alone, with its normal differentiation dependent on sex, it may be briefly stated that male distribution of pubic hair in the female suggests ovarian or pituitary disease, scanty normal distribution, pituitary or thyroid. Notably heavy normal distribution in the male suggests pituitary, female distribution the same gland or possibly the thyroid, while a scanty adornment of the pubes is found in both pituitary and thyroid disease. In addition, heavy pubic hair growth may be associated with disease of the adrenal cortex.

Eyes. With the exception of the mechanical effect of pituitary tumor, exophthalmos in hyperthyroidism (to which it is not exclusively confined) and cataract in diabetes, no specific and characteristic eye effects, demonstrable by routine examination, are traceable to endocrine influence.

Nose. Deviated septa, nasal discharges, and tender sinuses are frequently found throughout the endocrine series.

Teeth. Examination of the dentition serves to confirm the reports in the history. Actually the incidence of poor teeth is higher than the report in all the endocrine groups save that of the highly subjective ovarian failures; an endocrine association with poor dentition is apparent.

Tongue. Tremor of the tongue is not confined to the thyroid patients, although exhibited somewhat more frequently by them. The ovarian cases also show a relatively high frequency.

Tonsils. The earlier records showed an apparent endocrine association with tonsil infection, both in the reports of previous tonsillitis and of tonsil operations. Physical examination confirms and augments the earlier record, nearly twice as many endocrine as non-endocrine cases showing definite infection. This is the more striking as many more of the endocrine patients have had tonsillectomies. The recognition of infected tonsillar remnants should operate about equally in both major groups. An association is certainly proven; if it be causal or resultant remains to be resolved.

Thyroid Enlargement. The present findings were in some measure foreshadowed in the earlier comment on goiter. Actually, thyroid enlargement was observed as follows: Pituitary 18 per cent, thyroid 34 per cent, ovary 25 per cent, non-endocrine group 10 per cent. While the thyroid naturally leads, the occurrence is too frequent in the other endocrine groups for the observation to assume marked diagnostic meaning. Further, two-thirds of the proven thyroid cases did not show significant hyperplasia.

Breasts. Growth abnormalities of the breasts show a significant frequency only in pituitary disease, though under-development is associated fairly often with ovarian failure. The fat breast of the very obese male does not enter into this consideration as it is only one expression of the obesity.

Heart. Murmurs are significantly frequent in both pituitary and thyroid disease, while the ovarian cases show an even more striking absence of this sign.

Tachycardia characterizes the overactive and dysfunctional thyroid cases and in lesser degree, though not in frequency, the ovarian failures. Significant bradycardia is chiefly found in the hypothyroid group.

Abdomen. A generalized tenderness is characteristic of the hypersensitive ovarian failure. Its report in the obese is sometimes due to a well-meant enthusiasm in overcoming anatomical obstacles.

Male Genitalia. One in three of both the thyroid and pituitary groups show abnormalities such as general atrophy or hypertrophy, and undescended or atrophic testicles. The large incidence in the small male gonad group is to be anticipated, and in every positive case, not a castrate, was a post-orchitic atrophy following mumps. The overgrowth of the external genitalia in pituitary disease is the only feature of apparent single association.

Spine. Lordosis appears with significant frequency in the pituitary and thyroid groups and the few cases with kyphosis only in the former. Tenderness along the spine is reported in significant measure only in the gonad cases and is seemingly but one more instance of the dominance of a pain element in their picture.

Neuro-Muscular System. In the main, the weight of the significance of abnormality in this field lies in the suggestion of complication rather than of specific endocrine effect. Increased and diminished knee jerks are found in all groups and the percentile representation denies any specific influence of an individual gland.

Mental States. There were fewer cases of real mental retardation and more of psychosis in the endocrine than in the non-endocrine group. In the latter category the gonad and pituitary groups show a slight preponderance but not sufficiently to have differential significance. The field here is a new one to objective study and is of vital importance. It will form the topic of a later publication.

Personality. The prepubertal pituitary case is frequently that of a child with a behavior problem. Real mental retardation is found with certainty only in the Fröhlich syndrome; with many of the others, wandering attention is the real cause of the report. Many of these patients normalize spontaneously during the physiological readjustments of adolescence. In the really defective cases the glandular state may be no more than secondary to injury to the central nervous system. This is peculiarly true in patients with increased intracranial pressure.

In adult years, the pituitary cases, unless carrying an initial handicap as suggested above, include a large percentage of normal people and not a few whose intelligence is distinctly superior to the average. A small number show apathy, indifference, a heavy ill-nature, and mental sluggishness; they are less characteristic than those previously described.

While the cretin is the prototype of congenital thyroid failure, many children are found with hypoactive thyroids who depart definitely from the classic picture. They are mentally retarded or, at best, sluggish and are ill-natured with a heavy sort of negativism. They are incooperative and frequently asocial.

The personality in the adult thyroid case reflects in some degree the functional level of the gland. In the hyperactive and transition cases the subjects are tensely nervous and usually exhibit a marked degree of instability which translates itself into an easy irritability, fearfulness, and apprehension. Thyroid failure also results in a nervous instability which, however, finds expression in other terms. The subjects are self-centered, negativistic, and truculent, but the condition of ill-nature is of the type of a deep heavy anger rather than a sharp outburst. They resent the necessity of cooperation but manifest the reaction in a negative rather than positive form; they are sullen rather than aggressive.

Mental sluggishness is a fairly common feature of failure with myxedema and a normal mentality in the amyxedemic type is generally seen. The other function levels offer nothing distinctive.

In ovarian failure the subjects are insistently egocentric and that in a shrill and voluble fashion. They are highly incooperative and selfish but in a positive manner, the antithesis of the thyroid type. Their condition affords fertile soil for the growth of the major forms of hysteria.

The male castrate exhibits a profound mental depression but is otherwise normal. Even this inhibition has been known to be dissipated by the demonstration of a partial masculinity [see (4), Case B-42].

The social reaction in adrenal failure is conditioned by the very real asthenia that characterizes the disease.

SECTION II

Laboratory Measurements

The body of this portion of the paper will be devoted to a discussion of certain of the objective findings obtained by direct measurement or laboratory procedure. These form the group of objective facts on which the method of diagnosis is based. As previously stated, they are not competent in themselves to determine the diagnosis, but in addition to their important specific significance they offer fundamental criteria for the true evaluation of the more subjective portions of the study.

In the discussion of the clinical evidences it was usually possible to consider each endocrine gland as an entity, and only occasionally did the permutational influence of different function levels enter into consideration. With the present series of facts, on the other hand, amounts as well as directions are important, and many of the more valuable differential data derive their ultimate significance from the quantitative relation. On this basis the presentation of trends is both more significant and practical than that of actual averages, since the inclusion of incipient and early cases in a general series dilutes the differential values so strikingly exhibited in the established individual case.*

For purposes of definition "hypofunction" is used for that condition most certainly produced by surgical ablation of the gland, or with practically equal authority when it can ultimately be shown to have been destroyed by disease. Presumptively the like designation is correct in those functional states where the disease picture is identical in kind with that of demonstrated insufficiency.

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*In the subsequent discussion it will be understood that the statements refer only to experience in the human race. The delimitation of study to this group imposes certain obvious restrictions which, however, are more than compensated by the direct applicability of the results obtained.

"Hyperfunction" designates a condition in which all of the factual evidences are directly opposite to those characterizing the known hypofunctional state.

"Dysfunction" is that condition in which individual findings are found simultaneously which are associated with both augmented and depressed functional levels in the given gland. These may arise in transition states of functional involution or from different function levels in the several structures of the composite glands.

To save space and render the data more concrete, the significant facts may be presented in tabular form. Further, since trends are to be considered, simple symbols may be used which require a word of explanation.

For those measurements where the qualitative appearance of abnormal findings is the significant datum, the symbols + and 0 will be used in their usual connotation. The significance of the majority of the data, however, depends upon the direction and amount of departure from the level observed in health. It may be said that *all changes reported here are based upon comparison with the results of an elaborate series of control studies* conducted with groups of demonstrated healthy individuals.

The symbol > is used to designate increase, the magnitude of the tendency finding expression in the number of symbols used. The opposite symbol < indicates decrease, and uses the same conventions. The letter N indicates normal performance. When the tendency is variable the first symbol indicates the usual trend, the second a less frequent but still significant alternative.

In the tabulation only the hypofunctional states will be usually considered. Only the thyroid and pituitary, of the five glands under consideration, exhibit other function levels with certainty and significant facts associated with these latter will be treated in the text. Where mention is omitted it may be assumed that the findings for the higher function levels repeat those observed in failure.

Weight. Pituitary failure not only conduces to obesity but the tendency is more pronounced and the degree of overweight relatively greater than with the other glands.

TABLE III

PHYSICAL MEASUREMENTS
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Weight	> > >*	> > or <	N or >	N or >	< <
Lung Volume	N or <	< or < <	N or <	N	< < <
Temperature	N	<	N	N	N or <
Pulse	N or < sl.	< or < <	N or >	N or < sl.	N or sl. >
Respiration	N	< or N	N or >	N	N or >
Blood Pressure . . . Sys	< sl.	< or < <	< or < <	< sl.	< < or < < <
Dias	< sl.	< or < <†	< or < <	< sl.	< < or < < <
Alveolar CO_2	N	N	< <	N	<

*The Lorain-Levy type is a significant exception.
†See text.

Thyroid failure shows a similar but less marked tendency both in degree and kind. The subject of the associated type without myxedema is usually underweight and gains flesh under the normalizing influence of thyroid therapy.

Ovarian failure is more frequently associated with normal weight but a tendency to obesity is unmistakable though less pronounced. The male castrated in adult years shows a tendency to maintain a normal weight. Less frequently obesity of moderate degree is observed. If the basis of the mutilating operation were a wasting disease, as is frequently the case, some degree of underweight may persist for many years after the event. The fat eunuch is seemingly the product of a prepubertal emasculation.

The adrenal subjects, from the character of the underlying etiology of their condition, show a definite tendency toward emaciation. Obesity does not preclude the existence of Addison's disease but usually indicates an early stage of the condition [See (5) Case B-977].

Pituitary dysfunction determines a tendency to obesity only less marked than that of bilobar failure. The appearance of the condition in the hyperfunctional cases may be an evidence of beginning functional involution as the usual habit is a normal weight.

The thyroid shows a wide swing in weight extremes as the patient with hyperfunction shows an emaciation that is one expression of the increased metabolism. The dysfunctional patients are usually of normal weight, but may exhibit either some measure of emaciation as a residuum of earlier hyperfunction or an incipent obesity which foreshadows the approach of established glandular failure.

Lung Volume. This quantity, often picturesquely called the vital capacity, is readily determined with the spirometer, and has demonstrated a real significance.

Pituitary failure, even when coupled with a marked obesity, usually produces but minor downward changes in the quantity, and not a few subjects give readings even superior to the somewhat exacting normal standard. Hypofunction of the thyroid, on the other hand, uniformly lowers the observed value below that of prediction and in many cases far below that to be inferred from the general physical impairment. Ovarian failure follows the usual trend of the pituitary in sense and amount; the male gonad case is normal. Marked depression is noted in those adrenal cases in which the characteristic asthenia is well established, as in Addison's disease. It is much less marked in the group conventionally designated as ''hypoadrenalism.''

The test is peculiarly susceptible to subjective influences, and a lack of hearty cooperation may give values far below the truth. Hyperactive thyroid subjects perform as do the established failures; the dysfunctional group approach a normal level of performance.

Temperature. The body temperature is important both for suggestion of intercurrent disease, and for its direct influence on the basal rate interpretation. With the exception of the thyroid in marked degree, and the adrenal in much lesser measure, no specific endocrine influence is apparent. With thyroid failure there is a depression of the temperature of no uncertain proportions. Values below 97° and, rarely, below 96° have been recorded. The hypothyroid ''feels the cold'' and frequently the body temperature offers a partial explanation. This thermal effect apparently disappears in the other functional levels of the gland. While there may be a slight upward tendency in hyperfunction, it is far from marked and many of the patients are entirely normal in this respect.

Pulse. The pituitary failure shows a slight downward tendency which is rarely marked and frequently absent. This latter is not due to a nervous response, as measurements repeated daily over appreciable intervals and under non-disturbing conditions attest. The pulse of the thyroid failure is always slow, and in extreme cases values below 40 are not unknown. Where the functional condition is well established outside disturbing agents have but slight effect on the rhythm; in patients merging from an earlier dysfunction, excitement may produce a tachycardia which is transitory, as demonstrated by repeated observations. The ovarian cases give normal or somewhat increased pulse rates. The nervous instability so characteristic of these patients is certainly a factor in the latter. There seems to be, however, a true if slight accelerating impulse in the condition. Removal of the testicles, where any influence can be recognized, seems to exercise a slight slowing effect but it is never marked. The adrenal pulse is normal or slightly accelerated. A nervous element associated with the asthenia may exercise a causal influence.

At the other functional levels, the pituitary shows no more influence in dysfunction than in failure; in fact, a normal pulse is the prevailing observation. With the hyperactive gland, however, there is usually a slight acceleration and the prevailing rate somewhat exceeds the normal. With the thyroid, on the other hand, notable changes are produced. Tachycardia is one of the most charactertistic observations in patients with overactive glands, and very high rates are frequently recorded. The influence of the thyroid on the heart beat is unique among the endocrine glands, at least so far as degree is concerned. The dysfunctional thyroid may show rapid or slow pulse, depending largely on the degree of involution. The rapid pulse is the more frequent observation—in fact, in glands undergoing downward change a residual rapid pulse may be associated with a really significant depression of the basal rate. In the recessions characteristic of transition, the initially rapid pulse seems to lag behind all other evidences in reaching the terminal phase of established hypofunction. This point is of importance in the interpretation of otherwise contradictory data.

Blood Pressure. The actual levels of this important datum, especially the systolic pressure, are peculiarly at the mercy of extraneous nervous impulses. Dependable records, secured where necessary by frequent repetition, show the following relations.

Pituitary failure determines a slight drop in both the systolic and diastolic pressures which in the majority of cases is tendential rather than defined. The thyroid failure shows a depression always of concrete magnitude, and in many instances falls below 100 mm. for the systolic level. A definite exception is shown in the case of patients with long-standing myxedema where the arteriosclerotic changes characterizing the progress of this condition may raise the initially low blood pressures to normal or even hypertensive levels. The ovarian failure habitually records blood pressure levels on a parity with those of pronounced thyroid failure. With basal rates but moderately depressed, and normal or accelerated pulse rate, there is in this fact a definite differential significance. Removal of the testicles seems to produce a slight lowering in blood pressure, one of the very few objective results seemingly associated with the condition, but possibly an aftermath of the initial disease condition.

The hypotensive levels of adrenal failure are characteristic, and in conditions of like severity far more pronounced than those resulting from any other endocrine failure. Pituitary dysfunction repeats the levels observed in failure, but in hyperfunction a tendency toward hypertension has been recorded. The complication of many of these with demonstrated renal involvement raises a question that can not now be answered. Thyroid dysfunction shows a normal systolic and low diastolic pressure producing a pulse pressure above the normal. In hyperfunctional states this becomes even more marked as the systolic pressure tends toward hypertensive levels, while the diastolic remains normal or below. This pulse pressure is seemingly characteristic—at least, no other endocrine condition exhibits it systematically.

Alveolar Carbon Dioxide. This is another measurement dependent on cooperation. Thyroid levels are slightly below those of pituitary failure but both are normal. The male gonad shows no influence, and there is a slight downward tendency in adrenal disease, possibly traceable to a mild retention acidosis. Ovarian hypofunction frequently produces a drop of significant proportions suggestive of a mild acidosis of which, however, any other evidence is lacking. The same condition is found in pregnancy. Hyperthyroid patients may exhibit a slight depression, possibly a minor result of a slight but permanent overventilation.

TABLE IV

URINE MEASUREMENTS
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Volume	N or >	<	N or <	N	<
Elimination	N	< <	<	N	< <
Albumin	O	+	O	O	+
Casts	O	+	O	O	+
Sugar	Rarely*	Rarely*	+	O	+
"Indican"	N	>	>	N	N
Epithelial Debris	N	>	> >	N	>
"Urobilinogen"	+	O	O	O	O
Nitrogen Elimination	N	<	<	N	< <
Residual Nitrogen	N or >	> >	N or >	N	>
Phthalein Elimination	N	< <	<	N	< <
Salol Elimination	N	< or < <	<	N	< <
Urea Curve	N	N	N	N	< <
Urea Index	N	N or <	N	N	< <

*Glucose. See text.

Volume. Waiving all controversial discussion of causative factors, it is a matter of record that normal or increased urine volume is the usual finding in all functional levels of pituitary disease.

Thyroid failure depresses the volume and may produce an oliguria. The condition is manifest in all the functional stadia. Patients with ovarian failure show low normal values or those even below this somewhat elastic limit. This is not a result of sex habit as the female pituitary cases do not show it. The testicular failure shows a normal volume. Lowered adrenal activity exercises a marked depressing effect at least equal to that shown by thyroid failure.

Elimination. This is gauged somewhat uncertainly from joint consideration of the volume and the specific gravity. Pituitary cases are normal, the bulky urines indicating a hydruria rather than a true polyuria.

The thyroid patients show poor elimination even at the increased metabolic levels of hyperfunction.

Ovarian failure determines a fair level of elimination which falls between those of pituitary and thyroid disease. The male gonad patients are normal. In adrenal failure there is marked depression which is attributable in part to the real renal impairment associated with this condition.

Albumin and Casts. These evidences of renal involvement are certainly associated only with thyroid failure and dysfunction, and adrenal failure. Less certainly, patients with hyperpituitarism exhibit these evidences of kidney disturbance. The implications of a possible association have already been noted (See blood pressure). While the end results are the same, the thyroid evidences of renal disease seem to rest on a "pseudonephritis" (3), while the adrenal data come from a true nephropathic condition.

Glycosuria. The presence of sugar in the urine opens up an interesting and important chapter in the metabolic influences of the endocrine group. Discussion will be curtailed here as the whole question is being discussed elsewhere (11). The facts are too pertinent, however, to be passed over without some mention.

Glycosuria is a most infrequent finding in an established pituitary failure. Where observed it may derive from an intercurrent non-endocrine condition, or possibly, at times, be a residual effect of an earlier over-active posterior lobe. As is well known, increased sugar tolerance characterizes failure of this lobe, and in the cases of this series showing glycosuria, there was a uniformly raised tolerance for galactose, the sugar used for testing. The metabolism of glucose and galactose are not identical, however, and in this fact may lie the explanation. It may be enough here to repeat that a glycosuria—which is always very slight—is a most infrequent accompaniment of pituitary failure.

Just as pituitary failure raises sugar tolerance, so does that of the thyroid but in much less marked degree. A priori, one would anticipate a freedom from glycosuria in this condition as well. Actually, it is occasionally observed though with a marked infrequency. Hepatic dysfunction has been shown to be a fairly common complication of thyroid failure, and to this latter influence may be traced a large portion of the recorded glycosurias. Residua of dysfunctional conditions patently account for some of them. A third and tentative suggestion has been discussed elsewhere (3).

Slight glycosuria is a common finding in ovarian failure; the testicle is without influence on the sugar metabolism in adult years.

Glycosuria is a very common finding in adrenal failure and a marked lowering of sugar tolerance the apparent background. This runs counter to the usually proffered dictum that adrenal failure raises sugar tolerance but the customary basis for this opinion rests on a post hoc propter hoc argument involving the influence of suprarenin on blood sugar levels. Actually, the cases of Addison's disease show a profoundly depressed sugar tolerance and equally a slight and persistent glycosuria.

Since the usual type of pituitary dysfunction is that characterized by posterior lobe overactivity, it follows that glycosuria is a frequent observation in this condition. With less frequency it is recorded in cases of thyroid dysfunction for the reasons noted above. Hyperfunction of both glands frequently is associated with a slight persistent glycosuria. As the sugar tolerance in both is depressed, greatly with the pituitary, significantly with the thyroid, such a condition is to be anticipated.

For a discussion of the non-endocrine causes of glycosuria, the reader is referred to the paper just cited (11).

"Indican." The amount of this indoxyl derivative is usually regarded as a rough index of the degree of intestinal putrefaction. The constipated subjects of thyroid or ovarian failure frequently show an increase, and it is also noted less frequently in hyperpituitarism and thyroid dysfunction.

Epithelial Debris. While squamous cells and other epithelial detritus are always to be observed in the urine sediment, increased amounts are found in both thyroid and adrenal failure and even more strikingly in hypofunction of the ovary. The dysfunctional thyroid case is similar to that with failure.

"Urobilinogen." The presence of this pigmentary body in the urine has been primarily associated with hepatic disease. The color test for its identification is probably not specific for a single chemical entity. A positive response is frequently shown in pituitary disease. Its appearance with the other endocrinopathies is directly traceable to the presence of an intercurrent condition of which hepatic dysfunction and primary anaemia are the most significant.

Nitrogen Elimination. Determination of the total amount of nitrogen in the 24-hour urine serves several essential purposes. It is the one sure index of the actual level of protein catabolism, a physiological factor influencing profoundly a variety of functional levels. No wholly just interpretation of a patient's basal rate is possible without the check given by a knowledge of the daily protein utilization. It is an essential objective check on the truth of professed dietary restriction, and a settled asthenia may find its cause in a protein metabolism below a maintenance level (12), a condition far more common than is generally recognized.

Patients with pituitary failure and, of course, testicular deficiency, show a normal nitrogen output. Of the remaining three, all show a lowering which in the case of the ovarian failure is in part traceable to dietary considerations. The thyroid patient may have a poor appetite but failure to absorb is also a presumptive factor. The asthenic adrenal case marshals all of the inhibiting agencies, including some measure of retention, as these latter show uniformly a poor elimination of very real degree. With the thyroid only the hyperfunctional level with its selective influence on protein catabolism shows a normal elimination.

Residual Nitrogen. As the writer has shown, the residual nitrogen fraction in the urine of patients with endocrine disease —and a number of non-endocrine conditions—shows a definite tendency to exceed those limits first defined by Folin's (13) fundamental studies. He has further shown (14) that this derives not only from increase in substances normally present in small amount in the urine, but also from the presence of nitrogen containing substances of unknown origin and composition. Due care must be taken to consider the total output of nitrogen, as the fraction is apparently a summation of endogenous materials not primarily dependent on the nitrogen intake and so it shows a rising percentage with falling nitrogen elimination. The boundary adopted is applicable when the total nitrogen exceeds 5 grams, a level determining a very definitely inadequate protein exchange.

In pituitary failure a normal value is frequently encountered although the percentage showing an upward tendency is appreciable.

Thyroid failure is characterized by values superior to the upper normal limit and may reach large degrees of excess. The same is true of adrenal failure though only in the later stages of Addison's disease do the values obtained exceed in amount those of hypothyroidism. The ovarian case simulates the pituitary although the percentage of normals is slightly less. The testicle seemingly does not influence this factor, the usual recorded level being wholly within normal limits. At the upper function levels the pituitary shows an increased tendency toward higher values which in the hyperfunction group becomes a confirmed super-normal elimination. How far the complicating renal condition—which independently may cause a high residual —is responsible, can not be said at present. With the thyroid patients the upward tendency in both frequency and degree becomes more pronounced and reaches a maximum at the clear-cut hyperfunctional level.

Phenol-Sulphone-Phthalein. The high hopes held at the time of its introduction for the specificity of this test have unfortunately not been realized.

Failure of the pituitary and of the testicle do not depress elimination to any characteristic extent, but the similar function level of both the thyroid and adrenal exercises a definite downward influence. Ovarian failure falls in an intermediate position—a downward tendency being manifest but not pronounced. At the upper levels of function the thyroid shows a normalizing tendency which becomes established in the hyperactive state.

Salol. The test is very rough and primarily indicates the degree of permeability of the kidney. It agrees with the results already noted for the "phthalein" test.

Urea Curve. This derives from the administration of a test meal of pure urea and the estimation of the urea output for one two-hour period before, and four after ingestion. Delayed elimination and retention are shown very clearly by the test. Those cases with failure of the pituitary, testicle, and ovary, tend to show approximately normal curves. The point of real interest rests in the fact that the thyroid case with other evidences of kidney impairment here shows a normal picture, while the adrenal case with a true nephropathic condition shows very real retention.

Urea Index (15). This datum is an embodiment of the substance though not the form of the MacLean index. In the main it follows the indications of the urea curve. An interesting departure is found in thyroid failure where the somewhat high blood urea values (see later) exercise a downward tendency on the arithmetical expression of the coefficient. The adrenal lowering is a real evidence of the retention conditioned by the renal state in this disease.

TABLE V

BLOOD CHEMISTRY
ENDOCRINE HYPOFUNCTION

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Non-protein Nitrogen..........	N	>	N	N	>
Urea Nitrogen..................	N	>	N	N	>
Uric Acid......................	>	N	N	N	>
Creatinin......................	N	N	N	N	N
Residual Nitrogen.............	N	N	N	N	>
Sugar..........................	N	Low N	N	N	<

For a number of reasons that need not be considered here, discussion is limited to but a few of the many substances that go to make up this highly complex mixture.

Non-Protein Nitrogen. As an index of the amount of circulating nitrogen, the summation of the many products of both anabolism and catabolism, this quantity is highly important. In interpreting the values due consideration must be given to the level of protein metabolism as shown by the urine nitrogen. Variations in the latter will produce similar although smaller changes in the former (unpublished data).

The patients with pituitary and gonad failure show normal levels; those with thyroid and adrenal hypofunction, a moderate increase above the normal. This statement, of course, must be modified in the terminal phase of Addison's disease, in which the total picture of the blood nitrogen reflects the grave renal condition which coexists. Patients with thyroid dysfunction show a moderate upward tendency but the hyperfunction case manifests an opposing influence and the levels recorded are apt to be low in relation to the level of protein metabolism. The high values in hyperpituitarism are referable to the kidney condition already noted and which remains to be proven a characteristic feature of the condition.

Urea Nitrogen. This fraction commonly shows the same fluctuations as does the total nitrogen. The sole exception is in thyroid disease in which the dysfunctional group is as apt to be normal as to follow the upward trend of the total nitrogen, and in hyperfunction where urea is normal and non-protein nitrogen low.

Uric Acid. Of the hypofunctional group only pituitary and adrenal cases show an increase in uric acid above the normal. In the first it is seemingly the expression of a specific influence of the gland on some phase of purin metabolism. In the second it is merely one more evidence of an existing nephrosis. The consistently normal picture of the blood nitrogen in gonad failure, the equally consistent increase in all factors in adrenal disease, the high uric acid coupled with other normal values of pituitary hypofunction, and the directly opposite condition in hypothyroidism, form a really significant group of differential findings. High uric acid persists in all levels of pituitary disease and remains normal throughout the thyroid groups.

Creatinin. The values are normal throughout.

Residual Nitrogen. Just as summation of the several nitrogen-containing constituents in the urine shows a residual fraction to be accounted for, so in the blood a like procedure demonstrates an undetermined portion. Further, while the urine fraction is a very modest proportion of the whole, in the blood it is second only to urea in amount and may be 40 per cent or more of the total. Only in adrenal disease does this value exceed the normal, and an equally unique finding is the low value in hyperthyroidism. The relationships throughout the thyroid and adrenal groups of the blood and urine residual fractions offer additional support to the thesis that the kidney change in thyroid disease is apparent, and in adrenal failure, real.

TABLE VI

Blood Morphology
Endocrine Hypofunction

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Haemoglobin..................	N	Low N	N	N	<
Erythrocytes.................	N	< sl.	< sl.	N	<<
Color Index..................	N	N	N	N	>
Leucocytes...................	N	N	N	N	N
Polymorphonuclear Neutrophiles	N	N or <	N or sl. >	N	<
Lymphocytes..................	> or N	>	N or >	N or >	>>
Eosinophiles.................	> or N	N	N	N	>
Endothelial Leucocytes.........	N or <	<	N	N	N

Sugar. The importance of this constituent in the diagnosis and treatment of diabetes has focussed scientific attention, and a vast literature, recording and polemical, is the result. None of the many moot questions may be considered with propriety at this time. Pituitary and gonad failures are associated with normal levels, thyroid failure produces a moderate downward tendency but the values remain within conventional normal limits and only adrenal disease is consistently associated with levels below the normal. This latter fact is a diagnostic point of significance.

Haemoglobin. Normal values are associated with pituitary and gonad failure, low normal with hypothyroidism, and only adrenal disease consistently determines values suggesting anaemia. Hyperthyroid patients show normal levels and those with pituitary overactivity may exhibit high normal values.

Erythrocytes. The red cell count in pituitary and testicular failure is normal. Ovarian hypofunction conditions a slight downward tendency that is not to be refererd to a sex influence. With the thyroid failure there is also a downward tendency which parallels that of the haemoglobin. Adrenal failure determines a lowering of the number of the red cells which is even more pronounced than that of the haemoglobin. Pituitary hyperfunction is associated with a slight upward tendency to the erythrocyte count which follows that of the haemoglobin.

Color Index. The fluctuations of this quantity can be predicted from those of the two foregoing factors of which it is an arithmetical expression. The values remain normal with the sole exception of those in adrenal failure, where the fall in the erythrocytes exceeds that of the haemoglobin and produces an index approaching if not equalling 1.00.

Leucocytes. The values drawn from some 4,000 cases show prevailing normal averages throughout. Abnormality usually derives from some intercurrent condition.

Polymorphonuclear Neutrophiles. Normal values prevail in pituitary and testicular failure though an occasional high percentage is found in the former. Thyroid values are normal or depressed; ovarian, normal or slightly increased. The adrenal failures show the most definite relative decrease. Higher values are shown in pituitary dysfunction, and yet higher in hyperfunction. The same trend is shown by the higher thyroid levels but it is less marked in frequency and amount.

Lymphocytes. This division of the formed elements seems most susceptible to an endocrine influence. In pituitary failure a slight relative increase is usually found though many of the blood pictures are normal. Both ovarian and testicular failure are usually normal but both may show increase, the latter another of the rare instances of departure from the normal in the male hypogonad. A definite lymphocytosis prevails throughout the thyroid group and to an even more marked degree and extent in cases of adrenal failure. Pituitary dysfunction shows a tendency toward lymphocytosis more strongly than at the other function levels.

Eosinophiles. Pituitary failure and dysfunction show a slight eosinophilia, and a similar condition is found among the adrenal cases. A possible tendency in the dysfunctional thyroid group is scarcely significant.

The other blood elements do not need discussion.

In the next table are considered the data from two independent tests. These are dealt with together because their joint indications, from the directional and quantitative standpoints, are of the greatest significance in endocrine diagnosis. The observations in question are the so-called basal metabolic rate, and the assimilation limit for galactose.

Before passing to the discussion, stress may be laid on the difficulty in securing a true basal rate and the necessity for so doing if the record is not to be harmfully misleading. Many pages could be written on this point but space forbids.

The second test has been described elsewhere in detail (16) and needs no discussion here.

TABLE VII

Basal Metabolism and Sugar Tolerance

Endocrine Hypofunction

Observation	Pit.	Thy.	Ov.	Tes.	Adr.
Basal Rate	<	<<<	<	N or < sl.	<<
Sugar Tolerance	>>>	N or >	<<	N	<<<

Hyperfunction

Observation	Pit.	Thy.
Basal Rate	>	>>>
Sugar Tolerance	<<<	N or <

Pituitary failure lowers the basal rate, and in severe uncomplicated cases may reach a level of about 25 per cent below prediction. As is well recognized, failure of the thyroid produces a change, like in direction but far greater in amount. Values for this datum of —60 per cent have been recorded though needless to say the average case of hypothyroidism will fall significantly short of this greatest magnitude. The ovary exercises an influence identical with that of the pituitary in direction and about the same in magnitude. A considerable series of castrates reported elsewhere (4) ranged from —7 per cent to —23 per cent with a group average of —14 per cent. When the disturbing effect of nervous instability on the basal rate is considered, the values will be seen to compare well with the pituitary group who are less susceptible to this disturbing outside effect.

If the testicle in adult years has any direct influence on the level of oxygen requirement, it is at best a very slight one. A series of male castrates gave an average depression of —8 per cent, and the lowest of the composing members was but —11 per cent, certainly not an index of significant hypofunction. Adrenal failure, as indicated by proven Addison's disease, produces a lowering of the basal rate more significant than that of pituitary failure but falling far short of the levels which the thyroid can produce. Values in the minus thirties are recorded in severe cases. That the asthenia of the condition and its influence on appetite play some part in the production of the lower figures would seem to be certain. As these factors are characteristic of the disease state, the basal levels may be regarded as equally characteristic. Only the two limiting conditions need be considered as the dysfunctional states are merely algebraic summations of the opposing influences.

Hyperfunction of the pituitary is associated with a directional influence opposite from failure and of relatively the same moderate amount, +35 per cent approximately the upper limit of genuinely basal measurements.

Overactivity of the thyroid likewise produces an increase in the basal rate and this is usually about the same in relative degree as the depression of thyroid failure. Values above +100 per cent are recorded with a relative frequency. The writer's maximum value, made under basal conditions, is +87 per cent, and this phase of thyroid activity is less well represented in his series than are the other functional levels.

Turning to the sugar tolerance, a series of equally informative quantitative and directional differences are observed. Pituitary failure (posterior lobe) raises the assimilation limit for sugar far higher than does any other condition known to the writer. Upper levels of +300 per cent have been noted, the relatively small normal dosage of galactose permitting the measurement of such massive increases. Thyroid failure produces an upward tendency but it is never pronounced. Roughly, two-thirds of the cases will show a normal tolerance, and in patients with failure and uncomplicated by established renal disorders, such increases as are recorded are of the order of +25 per cent to +50 per cent. The average deviation for a long series of those showing increase is +33 per cent. Ovarian failure (or castration) lowers sugar tolerance at most to 20 grams, the prepubertal level. Of the several hundred cases in this series none has shown a level lower than this unless in the presence of some intercurrent and unrelated disease condition itself capable of influencing sugar metabolism.

Removal of the testicles in adult years has no influence on the uniform assimilation limit shown by the healthy male throughout his life, and functional failure is equally without influence. Adrenal failure, on the other hand, lowers the assimilation limit of galactose to a very marked degree, and in some cases a dose of five grams is enough to produce a definite melituria in an otherwise sugar-free patient.

Hyperpituitarism lowers the assimilation limit for sugar as markedly as failure raises it. It seems probable that the quantitative level of the tests discussed in this section are relative indices of the degree of the severity of the involvement. In long-continued observation in individual untreated pituitary cases the writer has been able to trace the gradual transition from initial overactivity to a final complete failure as shown by the galactose tolerance in connection with repeated comprehensive studies of other indices.

Hyperthyroidism affects sugar tolerance in opposite sense and usually in like degree as glandular failure. Occasionally a case is observed in which, however, a really significant depression of the sugar tolerance is found in this condition. The fact has been discussed elsewhere (3).

The discussion of the several non-endocrine influences that may simulate or confuse the individual endocrine picture must be reserved for a later communication.

One very definite possibility for confusion within the endocrine group comes in the two conditions of ovarian failure and that most common type of pituitary dysfunction in which the anterior lobe is under-active while the posterior lobe over-active. To clarify discussion and emphasize alike the similarities and divergences, data from two synthesized representative cases may be briefly presented.

TABLE VIII

Pituitary Dysfunction and Ovarian Failure

	Pituitary	*Ovary*
Sex	Female	Female
Age	31	31
Weight Deviation	+30%	+20%
Lung Volume Deviation	—10%	—10%
Basal Rate Deviation	—18%	—18%
Temperature	98.2°	98.2°
Pulse	66	78
Respiration	15	15
Blood Pressure, Sys.	116 mm.	102 mm.
Blood Pressure, Dias.	76 mm.	70 mm.
Alveolar CO_2	45 mm.	37 mm.
Urine, Volume	1300 cc.	1000 cc.
Specific Gravity	1.018	1.013
Albumin	0	0
Casts	0	0
Sugar	+	+
Indican	N	>
Urobilinogen	+	0
Total Nitrogen	11.00 gm.	8.00 gm.
Residual Nitrogen	8.3%	8.3%
Non-Protein Nitrogen	33 mgm.	33 mgm.
Uric Acid	4.0 mgm.	3.2 mgm.
Sugar Tolerance	—50%	—50%
Haemoglobin	93	92
Lymphocytes	38%	29%
Eosinophiles	3%	1%

A curstory survey of the table shows that the real points of difference are pulse, blood pressure, alveolar carbon dioxide, urobilinogen, total nitrogen, blood uric acid, lymphocytosis, and eosinophiles. Patently, two such cases would offer no difficulty in their differentiation but the elimination of some of the more distinctive features as, for example, the urobilinogen and alveolar carbon dioxide, might leave the conclusion in doubt. Such a condition is not uncommon, and in such case the facts of the history and physical examination furnish most valuable differential data. Finally, again these may fall short of sharp definition and a tentative diagnosis based on probability be the outcome.

By way of illustrating in a simple way the use of the foregoing data in diagnosis an ideal case of each of five uncomplicated endocrine failures may be assumed. Each patient is a young adult and the degree of gland failure is the same in each case. It must not be forgotten, however, that in the actual use of this schema, each datum must be considered in the setting in which it occurs. Ideal uncomplicated cases are the exception here as they are throughout the realm of medicine.

TABLE IX

Illustrative Data in Hypothetical Ideal Cases

	Pit.	Thy.	Ovary	Test	Adr.
Basal Rate	—25%	—45%	—18%	—6%	—35%
Pulse	68	50	78	72	76
Respiration	14	10	16	15	15
Temperature	98.2°	97.0°	98.2°	98.4°	97.8°
Blood Pressure, Sys.	110	100	98	112	90
Dias.	70	60	65	75	60
Sugar Tolerance	+100%	±0%	—50%	±0%	—83%

Section III

Special Examinations

The purpose of this group of observations differs from that of the two preceding but rather in emphasis that in content. While the earlier considerations were devoted to the establishment of an endocrine diagnosis, always be it rememberd, only after non-endocrine causes had been eliminated, the present group deals with data primarily significant in demonstrating the presence or absence of complicating conditions of non-endocrine origin. Only occasionally and secondarily do these evidences bear directly on the establishment of an endocrine diagnosis. For reasons which will be obvious, the present brief discussion must be limited to these latter, adequate treatment of the entire field being reserved for later communication.

Eye Examination. As noted earlier in the text this is now a part of the routine examination of every case. Yellowish to yellow discs are found in one-half of the pituitary cases, and with less but significant frequency in those with ovarian failure. Enlargement of the blind spots is most frequently reported in adrenal disease, next in the pituitary group, and with significant frequency in the thyroid and ovarian cases and in a large group of non-endocrine disorders.

Contraction of form and color fields of various patterns are associated with both endocrine and non-endocrine conditions. Temporal cutting with pituitary tumor is but one of several and certain of these dealing severally with: (a) cutting of the upper quadrant of the form fields, (b) concentric contraction of form and color fields, and (c) the field changes in pregnancy are shortly to be discussed elsewhere by the writer and his associates (17).

Barany Test. Postive findings have been reported in several cases of thyroid failure complicated by hepatic dysfunction (18).

Electrocardiogram and Heart Examination. In spite of the well-established influence of thyroid disease on cardiac rhythms, the proven incidence of cardiac disease associated with thyroid failure is significantly less than with either the pituitary or gonad groups (19). Further, the total endocrine incidence is much less than in the complementary non-endocrine series.

Gastric Examination. This consists both of the analysis for free acid and of the neutral red test. One case of Addison's disease gave no free acid and failed to show the dye at the end of two hours. Primary anaemia was ruled out. A single case is not significant but the fact is reported for a possible later interest.

Liver Function Test (McClure) (20). This test is chiefly interesting for its demonstration of hepatic dysfunction in a fairly large number of cases of thyroid failure (3).

Pelvic Examination. The demonstration of pelvic hypoplasia as a possible stigma of earlier endocrine disease, of genital abnormalities and of gross ovarian disease are the principal features of glandular significance. A very low incidence of organic ovarian change coupled with the impressive record of functional derangements is the most significant fact elicited.

Orthopedic Examination. The findings are directly significant for the endocrine group only in the delineation of developmental defects possibly attributable to glandular disorders.

Psychometric Examination. A notably high relative incidence of feeble-mindedness was demonstrated in the thyroid group. The remaining endocrine cases were associated with pituitary disease.

Psychiatric Examination. A significant number of endocrine patients were demonstrated to have a psychosis. The question of interrelationship cannot be considered here.

Neurological Examination. The simulation of endocrinopathy by various types of nervous disease is one outcome of this phase of study. The principle return is the specific significance to the individual case.

Roentgenological Examinations. (a) Skull. Enlarged diploic veins and marked convolution impressions are most frequently found in the pituitary group, though well represented in all of the others. Their suggestion of intracranial pressure are significant in a possible direct influence on pituitary activity.

(b) Sella. In the delineation of this structure so intimately connected with one of the ductless glands, one would initially assume a direct and important association. Further consideration, however, lessens the potential significance in view of the fact that but a small percentage of functional aberrations are associated with tumor growth. When further the amply supported fact is considered that bony structures associated with functionally normal glands are not sharply delimited as to shape or size, the real significance of the finding resolves itself into the demonstration of actual destruction of bone with the associated inference of glandular hyperplasia. An appreciable number of the pituitary cases show abnormalities of the sella, some with erosion and some with clinoid bridging, the latter not a normal finding but equally not explicitly defining disease of the gland.

Further, in the examination of a series of 250 non-endocrine patients, 8 showed bridging, 9 a thickening of the clinoids, and 2 were reported with "notably small" sellae.

It would seem fair to deduce from these facts (and from uniformly confirmatory evidence drawn from the results of much larger series) that reliable evidence of clinoid erosion is very significant, and depending on the site involved, indicates either pituitary or extra-sellar tumor. Beyond this clear-cut indication but little specific information derives from radiographic study of the structure.

(c) Pineal. The observation of calcification of this structure is a by-product of the radiographic study of the head. The phenomenon has been observed in endocrine (1.6 per cent) and non-endocrine (1.8 per cent) cases alike. In none of them either in history, physical examination, or laboratory study was evidence forthcoming of those departures from the normal attributed by some to functional aberration of the gland. Like the more widely exploited structure, the testicle, objective evidence of significant endocrine activity in adult years is lacking.

The numerous other evidences from radiography deal with non-endocrine conditions and are valuable only for the individual case. An exception may be noted in the case of pyelograms.

This paper, itself a summary, cannot be condensed to a few conclusions. One point may be touched upon, however. The underlying principle of the study is not limited to the differentiation of the endocrinopathies themselves as a whole but one small chapter in the huge book of medicine. It is and should be applicable to the whole field of the diagnosis of disease, a prerequisite to, and primary step in, the determination of judicious and effective treatment.

Before the final word is written, a brief statement should be made. This paper concludes a series of reports which are the first formal presentation of studies begun in 1912 and prosecuted without remission ever since. In the compilation of the data, many thousands of records have been made ranging from single individual chemical analyses to the series of lengthy and carefully conducted interviews which furnish the basis of a psychiatric report. All of this material represents the accurate, sincere, interested labor of a large group of highly trained individuals. To them all, laboratory and clinical assistants, associates and colleagues, the writer can but acknowledge an indebtedness and an inspiration that cannot be expressed.

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Reprinted from ENDOCRINOLOGY, The Bulletin of the Association for the Study of Internal Secretions, 1214 Wilshire Medical Bldg., Los Angeles, California, Vol. 13, No. 4, July-August, 1929, Pages 327 to 362.